Transition-Metal-Free Intermolecular α-C-H Amination of Ethers at Room Temperature

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Supporting information

Experimental Section

1. Chemicals and Reagents

All manipulations were carried out under an inert N_2(g) atmosphere using standard Schlenk or glovebox techniques. Solvents were purified using a two-column solid-state purification system (Innovative Technology, NJ, USA) and transferred to the glove box without exposure to air. Deuterated solvents were purchased from Cambridge Isotope Laboratories, Inc., and were degassed and stored over activated 3 Å molecular sieves. THF-d_8 was purchased from ARMAR AG, and was degassed and stored over activated 3 Å molecular sieves. Unless otherwise noted, all other reagents and starting materials were purchased from commercial sources and used without further purification. Liquid compounds were degassed by standard freeze-pump-thaw procedures prior to use. Tetrahydropyran and 2-methyltetrahydrofuran were distilled from stabilizers before use. Dry 1,2-dimethoxyethane was purchased from Aldrich and used without purification. Diphenyl iodonium hexafluorophosphate and triflate were purchased from ABCR and Aldrich correspondently. 2,2-Dimethylpent-4-en-1-amine was synthesized according to literature procedure.[1] Other amines were purchased from commercial sources. Sulfonamides[2], amides and trifluoroacetyl amides[3] were prepared from corresponding amines by standard methods. 3-(4-methoxybenzyl)-5-methylpyrimidine-2,4(1H,3H)-dione[4] and di-tert-butyl 5-fluoro-2,4-dioxopyrimidine-1,3(2H,4H)-dicarboxylate[5] were prepared according to known procedures.

2. Physical methods

The ^{1}H and ^{13}C NMR spectra were recorded at 293 K or 373 K on Bruker Avance 400 spectrometers. ^{1}H NMR chemical shifts were referenced to residual solvent as determined relative to Me_4Si (δ = 0 ppm). The $^{13}C\{^1H\}$ chemical shifts were reported in ppm relative to the carbon resonance of $CDCl_3$ (77.16 ppm), DMSO-d_6 (39.52 ppm), CD_2Cl_2 (53.84 ppm) or CD_3CN (118.26 ppm). GC measurement was conducted on a Perkin-Elmer Clarus 400 GC with a FID detector. HRESI-MS measurements were conducted at the EPFL ISIC Mass Spectrometry Service with a Micro Mass QTOF Elemental analyses were performed on a Carlo Erba EA 1110 CHN instrument at EPFL.

3. General procedures for the entries reported in Table 1

Entries 1-10, 18-20

Sodium hydride (60% dispersion in mineral oil, 10 mg, 0.25 mmol, entries 1-7) or corresponding base (0.25 mmol, entries 8-10) was added to a stirred solution of N-benzylmethanesulfonamide (46 mg, 0.25 mmol) in 1 mL of dry tetrahydrofuran at room temperature under nitrogen. After stirring for 1 hour an oxidant (0.3 mmol) was added slowly and the reaction mixture was left stirred for 10 hours. In entry 5 no oxidant was added; instead a balloon with O_2 was connected to reaction vessel. After the indicated time, the reaction mixture was analyzed by GCMS using 30 μL of dodecane as an internal standard.

Entries 11-17

Sodium hydride (60% dispersion in mineral oil, 10 mg, 0.25 mmol) was added to a stirred solution of N-benzylmethanesulfonamide (46 mg, 0.25 mmol) and dry tetrahydrofuran (0.18 g, 2.5 mmol) in 1 mL of the corresponding solvent at room temperature under nitrogen. After stirring for 1 hour Ph_2IPF_6 (128 mg, 0.3 mmol) was added and the reaction mixture was left stirred for 10 hours.

4. The procedures for the preparation of starting materials

General procedure for the preparation of sulfonamides (1a-1m)

To a stirred solution of primary amine (20 mmol) and pyridine (2.37 g, 30 mmol) in CH_2Cl_2 (50 mL) at 0° C a corresponding sulfonyl chloride (20 mmol) was slowly added. The reaction mixture was slowly warmed to room temperature and stirred for 12 hours, then the reaction was quenched with water (30 mL), extracted with CH_2Cl_2 (2x50 mL) and washed with water. The organic phase was dried over anhydrous Na_2SO_4. The solvent was evaporated to afford the product. If needed, crude product was purified by silica gel flash chromatography using mixture of ethylacetate/hexane as an eluent.

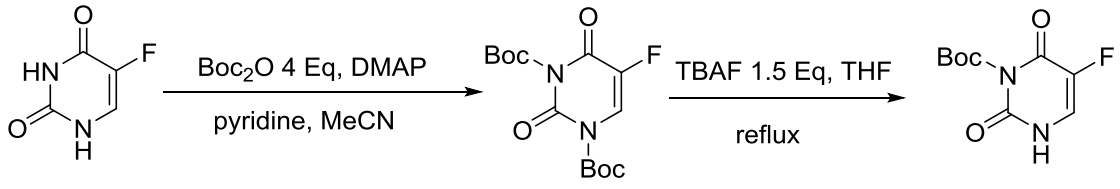
General procedure for the preparation of N-acetamides (2a-2d, 2i-2o)

20 mmol of the corresponding amine was dissolved in 50 mL of CH_2Cl_2 followed by the addition of triethylamine (3.03 g, 30 mmol) and dropwise addition of acetyl chloride (1.72 g, 22 mmol) at 0° C. After stirring for 10 hours at room temperature 30 mL of water was added to the reaction solution. The organic phase was separated and aqueous layer was extracted two times with 50 mL of chloroform, and the resulting organic layer was concentrated after drying with anhydrous Na_2SO_4 to obtain the product. If needed, crude product was purified by silica gel flash chromatography using mixture of ethylacetate/hexane as an eluent.

General procedure for the preparation of N-trifluoroacetamides (2e-2h)

20 mmol of the corresponding amine and pyridine (2.37 g, 30 mmol) were dissolved in 50 mL of dry CH_2Cl_2. Trifluoracetic anhydride (22 mmol 4.62 g) in 20 mL of CH_2Cl_2 was added slowly at 0ºC. The reaction was stirred overnight at room temperature, quenched with water, extracted twice with CH_2Cl_2 and washed with water. The organic layers were dried with Na_2SO_4, and the solvent was evaporated. The residue was purified by silica gel flash chromatography using mixture of hexane/ethyl acetate as an eluent.

Tert-butyl 5-fluoro-2,6-dioxo-3,6-dihydropyrimidine-1(2H)-carboxylate (9b)



5-Fluorouracil (3.9 g, 30.0 mmol), di-tert-butyl dicarbonate (26.2 g, 120 mmol), pyridine (5 mL), DMAP (100 mg, 0.8 mmol) and MeCN (50 mL) were stirred together for 12 h at room temperature. The reaction mixture was concentrated in vacuo, and the residue was partitioned between CH_2Cl_2 (100 mL) and water (100 mL). The organic layer was separated, and the aqueous phase was extracted twice with CH_2Cl_2 (2×50 mL). The combined organic layers were dried over $MgSO_4$ and filtered, and the solvent was removed by evaporation in vacuo. The residue was purified by recrystallization from Hexane-EtOAc (10:1) to afford 6.70 g (68%) of di-tert-butyl 5-fluoro-2,4-dioxopyrimidine-1,3(2H,4H)-dicarboxylate **(9b').**

Purified **9b'** (330 mg, 1 mmol) was dissolved under argon in 2 mL of dry THF. A 1 M solution of Bu_4NF (1.5 mL, 1.5 mmol) in THF was then added and the reaction mixture was refluxed for 8 h. After cooling to room temperature, water (20 mL) was added. After extraction with AcOEt (2×20 mL), the organic layers were washed with brine (10 mL), dried with Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude product was purified by gradient silica gel chromatography (hexane/AcOEt 10:1 to 1:1) to afford N3-Boc-5-fluorouracil as white powder 87 mg (38%).

5. General procedures for the intermolecular α-C-H amination of ethers

General procedure for the synthesis of N-(tetrahydrofuran-2-yl)sulfonamides (3a-3n)

To a suspension of sodium hydride (60% dispersion in mineral oil, 20 mg, 0.5 mmol) in 1 mL of dry THF a sulfonamide (0.5 mmol) in 1 mL of THF was added at room temperature under nitrogen. After stirring for 1 hour at room temperature Ph_2IPF_6 (256 mg, 0.6 mmol) was added and the reaction mixture was left stirred for 6 hours. The solvent was removed under reduced pressure and resulting solid was subjected to column chromatography (silica gel) to afford the product. For the new compounds, their ^1H and ^{13}C data were reported together with high resolution mass spectrometric data or elemental analysis.

General procedure for the synthesis of N-(tetrahydrofuran-2-yl)amides (5a-5o)

To a suspension of sodium hydride (60% dispersion in mineral oil, 20 mg, 0.5 mmol) in 1 mL of dry THF an amide (0.5 mmol) in 1 mL of THF was added at room temperature under nitrogen. After stirring for 3 hours at room temperature Ph_2IPF_6 (319 mg, 0.75 mmol) in 1 mL of THF was added and the reaction mixture was left stirred for 6 hours. The solvent was removed under reduced pressure and resulting solid was subjected to the column chromatography (silica gel) to afford the product. For the new compounds, their ^1H and ^{13}C data were reported together with high resolution mass spectrometric data or elemental analysis.

General procedure for the synthesis of phthalimide derivatives (5p, 8b, 8d)

To a suspension of potassium phthalimide (92.5 mg, 0.5 mmol) in 2 mL of corresponding alkyl ether Ph_2IPF_6 (256 mg, 0.6 mmol) was added and reaction mixture stirred at 40˚C or 60˚C overnight under nitrogen. The solvent was removed under reduced pressure and resulting solid was subjected to the column chromatography (silica gel) to afford the product.

General procedure for the α-C-H bond amination with N-heterocyclic amines (7a-7d)

To a suspension of sodium hydride (60% dispersion in mineral oil, 20 mg, 0.5 mmol) in 1 mL of dry THF an amine (0.5 mmol) in 1 mL of THF was added at room temperature under nitrogen. After stirring for 1 hour at room temperature Ph_2IPF_6 (319 mg, 0.75 mmol) was added and the reaction mixture was left stirred for 6 hours. The solvent was removed under reduced pressure and resulting solid was subjected to column chromatography (silica gel) to afford the product. For the new compounds, their ^1H and ^{13}C data were reported together with high resolution mass spectrometric data or elemental analysis.

General procedure for the α-C-H bond amination of various alkyl ethers (8a-8h)

To a suspension of sodium hydride (60% dispersion in mineral oil, 20 mg, 0.5 mmol) in 3 mL of dry alkyl ether an amide or sulfonamide (0.5 mmol) was added at room temperature under nitrogen. After stirring for 3 hours at room temperature Ph_2IPF_6 (319 mg, 0.75 mmol) was added and the reaction mixture was left stirred for 6 hours. The solvent was removed under reduced pressure and resulting solid was subjected to the column chromatography (silica gel) to afford the product. For the new compounds, their ^{1}H and ^{13}C data were reported together with high resolution mass spectrometric data or elemental analysis.

General procedure for the synthesis of nucleoside analogues (10a-10d)

To a suspension of sodium hydride (60% dispersion in mineral oil, 20 mg, 0.5 mmol) in 1 mL of dry alkyl ether and N3-protected nucleobase (0.5 mmol) was added at room temperature under nitrogen. After stirring for 3 hours at room temperature Ph_2IPF_6 (362 mg, 0.85 mmol) in 2 mL of ether was added and the reaction mixture was left stirred for 6 hours. The solvent was removed under reduced pressure and resulting solid was subjected to the column chromatography (silica gel) to afford the product. For the new compounds, their ^{1}H and ^{13}C data were reported together with high resolution mass spectrometric data or elemental analysis.

6. Mechanistic studies

Reaction in the presence of TEMPO

Sodium hydride (60% dispersion in mineral oil, 20 mg, 0.5 mmol) was added to a stirred solution of N-benzylmethanesulfonamide (93 mg, 0.5 mmol) in 1 mL of dry tetrahydrofuran at room temperature under nitrogen. After stirring for 1 hour TEMPO (7.8 mg, 0.05mmol) and Ph_2IPF_6 (256 mg, 0.6 mmol) was added, and the reaction mixture was left stirred for 6 hours. After the indicated time the reaction mixture was analyzed by GCMS using 30 μL of dodecane as an internal standard. **3a** was not detected.

Comparison of rate constants of the reactions of acetanilide (4d) with THF and THF-d_8

Four stock solutions were prepared: 405 mg of acetanilide and 102 mg of dodecane in 6.0 mL of THF (Solution A); 1.50 g of Ph_2IPF_6 in 5.0 mL of THF (Solution B); 405 mg of acetanilide and 102 mg of dodecane in 6.0 mL of THF-d_8 (Solution C); 1.50 g of Ph_2IPF_6 in 5.0 mL of THF-d_8 (Solution D). To 1.0 mL of Solution A 20 mg of sodium hydride (60% dispersion in mineral oil) was added and the mixture was stirred for 30 minutes. Then 1.0 mL of Solution B was added at once at room temperature (23,5 ˚C). The aliquotes of the reaction mixture were quenched with ethanol and analyzed by GC (calibration was performed using dodecane as an internal standard). The procedure was repeated with Solutions C and D. The ratio between both reaction rate constants was determined to be 4.60.

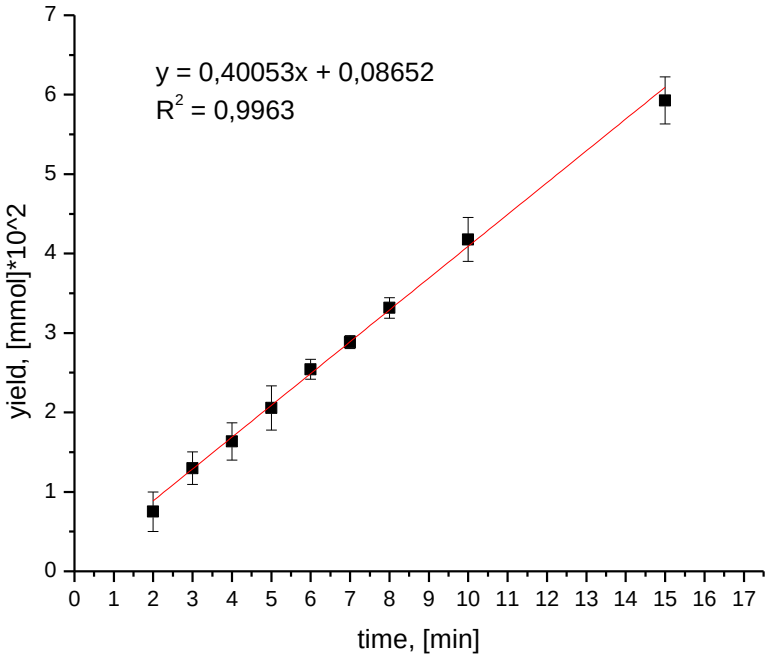


Figure S1. The rate of the reaction of acetanilide (**4d**) in THF

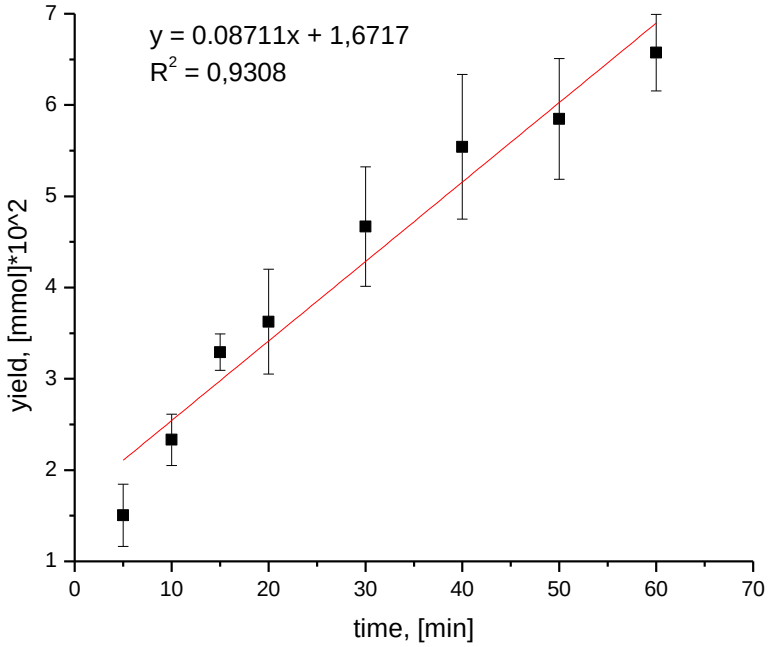
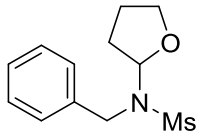
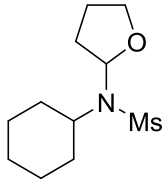


Figure S2. The rate of the reaction of acetanilide (**4d**) in THF-d_8

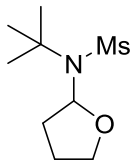
7. Detailed descriptions of the products



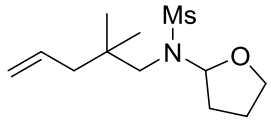
N-benzyl-N-(tetrahydrofuran-2-yl)methanesulfonamide (3a)
Isolated by gradient elution from the column with hexane-EtOAc (9:1 to 4:1) in 73% yield as a colorless oil.
^{1}H NMR (400 MHz, $CDCl_3$): 7.42 (d, *J* = 7.5 Hz, 2H), 7.37-7.34 (m, 2H), 7.30-7.26 (m, 1H), 5.72 -5.69 (m, 1H), 4.57 (d, *J* = 16.7 Hz, 1H), 4.27 (d, *J* = 16.7 Hz, 1H), 4.07-4.01 (m, 1H), 3.84-3.79 (m, 1H), 2.97 (s, 3H), 2.08-1.81 (m, 3H), 1.75-1.69 (m, 1H).
^{13}C NMR (101 MHz, $CDCl_3$): 138.3, 128.7, 127.5, 127.1, 88.8, 68.4, 46.6, 39.6, 29.6, 24.8.
HRESI-MS: calculated for ($C_{12}H_{17}NO_3S$, M+H), 256.1007; found, 256.1000.



N-cyclohexyl-N-(tetrahydrofuran-2-yl)methanesulfonamide (3b)
Isolated by gradient elution from the column with hexane-EtOAc (20:1 to 9:1) 76% yield as a colorless oil.
^{1}H NMR (400 MHz, $CDCl_3$): 5.34 (m, 1H), 4.05-3.99 (m, 1H), 3.77-3.73 (m, 1H), 3.38-3.31 (m, 1H), 2.98 (s, 3H), 2.19-2.02 (m, 3H), 1.92-1.60 (m, 8H), 1.34-1.08 (m, 3H).
^{13}C NMR (101 MHz, $CDCl_3$): 88.7, 68.1, 57.5, 43.4, 34.2, 31.4, 31.0, 26.6, 25.3.
HRESI-MS: calculated for ($C_{11}H_{21}NO_3S$, M+Na), 270.1140; found, 270.1143.

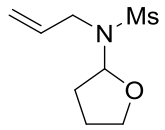


N-(tert-butyl)-N-(tetrahydrofuran-2-yl)methanesulfonamide (3c)
Isolated by gradient elution from the column with hexane-EtOAc (19:1 to 9:1) in 39% yield as a white solid.
^{1}H NMR (400 MHz, CD_2Cl_2): 5.33-5.29 (m, 1H), 4.08-4.03 (m, 1H), 3.74-3.69 (m, 1H), 2.99 (s, 3H), 2.51-2.44 (m, 1H), 2.12-1.99 (m, 2H), 1.88-1.79 (m, 1H), 1.43 (s, 9H).
^{13}C NMR (101 MHz, CD_2Cl_2): 90.6, 68.5, 59.7, 45.7, 32.9, 30.8, 25.8.
HRESI-MS: calculated for ($C_9H_{19}NO_3S$, M+Na), 244.0983; found, 244.0984.
Elemental analysis: Anal. Calcd for $C_9H_{19}NO_3S$: C, 48.84; H, 8.65; N 6.33. Found: C, 48.88; H, 8.35; N 6.15.

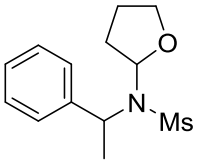


N-(2,2-dimethylpent-4-en-1-yl)-N-(tetrahydrofuran-2-yl)methanesulfonamide (3d)
Isolated by gradient elution from the column with hexane-EtOAc (6:1 to 4:1) in 78 % yield as colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): 5.88-5.78 (m, 1H), 5.32-5.03 (m, 3H), 4.11-4.06 (m, 1H), 3.81-3.76 (m, 1H), 3.24 (d, *J* = 14.7 Hz, 1H), 2.98 (s, 3H), 2.91 (d, *J* = 14.7 Hz, 1H), 2.54-2.45 (m, 1H), 2.22-2.10 (m, 2H), 2.03 (m, 2H), 1.89-1.82 (m, 1H), 0.95 (s, 3H), 0.94 (s, 3H).
^{13}C NMR (101 MHz, $CDCl_3$): 134.8, 117.8, 94.7, 77.2, 68.6, 59.6, 45.4, 40.8, 35.5, 31.7, 25.737, 25.3, 25.1.
HRESI-MS: calculated for ($C_{12}H_{23}NO_3S$, M+H), 262.1477; found 262.1472.

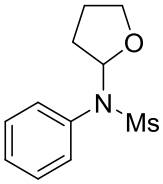


N-allyl-N-(tetrahydrofuran-2-yl)methanesulfonamide (3e)
Eluated from the column with hexane-EtOAc (9:1) in 77% yield as a colorless oil
^{1}H NMR (400 MHz, $CDCl_3$): 5.97-5.87 (m, 1H), 5.63-5.60 (m, 1H), 5.28 (dd, *J* =17.2, 1.4 Hz, 1H), 5.16 (dd, *J*= 10.2, 1.4 Hz, 1H), 3.99-3.93 (m, 1H), 3.82-3.78 (m, 3H), 2.93 (s, 3H), 2.13-2.05 (m, 1H), 1.98-1.85 (m, 3H).
^{13}C NMR (101 MHz, $CDCl_3$): 135.5, 117.1, 88.7, 68.2, 45.4, 39.7, 29.4, 25.0.
HRESI-MS: calculated for ($C_8H_{15}NO_3S$, M+Na), 228.0670; found, 228.0668.

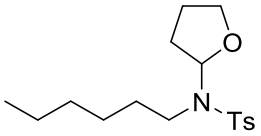


N-(1-phenylethyl)-N-(tetrahydrofuran-2-yl)methanesulfonamide
Isolated by gradient elution from the column with hexane-EtOAc (20:1 to 9:1) in 75 % yield as white solid. Diastereomeric ratio is 2:3 (**3f**:**3g**).
N-(1-phenylethyl)-N-(tetrahydrofuran-2-yl)methanesulfonamide (d.r- 2:3) major product (3f)
^{1}H NMR (400 MHz, CD_2Cl_2): 7.55 (d, *J* = 7.6 Hz, 2H), 7.38-7.27 (m, 3H), 5.48 (m, 1H), 4.89 (q, *J* = 7.24 Hz, 1H), 4.11-4.06 (m, 1H), 3.80-3.75 (m, 1H), 2.45 (s, 3H), 2.12-2.02 (m, 3H), 1.96-1.88 (m, 1H), 1.73 (d, *J* = 7.2 Hz, 3H).
^{13}C NMR (101 MHz, CD_2Cl_2): 140.1, 129.00, 128.5, 128.00, 89.3, 67.9, 54.6, 42.4, 30.8, 25.5, 21.1.
HRESI-MS: calculated for ($C_{13}H_{19}NO_3S$, M+Na), 292.0983; found, 292.0981.

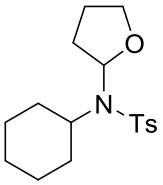
N-(1-phenylethyl)-N-(tetrahydrofuran-2-yl)methanesulfonamide (d.r- 2:3) minor product (3g)
Contains 15% of major isomer.
^{1}H NMR (400 MHz, CD_2Cl_2): 7.41-7.24 (m, 5H), 5.06-5.02 (m, 2H), 4.03-3.98 (m, 1H), 3.71-3.66 (m, 1H), 3.04 (s, 3H), 2.28-2.22 (m, 1H), 2.02-1.97 (m, 1H), 1.77-1.72 (m, 5H).
^{13}C NMR (101 MHz, CD_2Cl_2): 142.2, 128.7, 127.5, 127.4, 89.3, 68.5, 55.6, 53.8, 43.8, 31.34, 25.5, 17.9.
Elemental analysis: Anal. Calcd for $C_{13}H_{19}NO_3S$: C, 57.97; H, 7.11; N 5.20. Found: C, 57.64; H, 7.20; N 4.88.



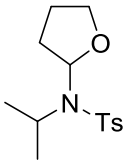
N-phenyl-N-(tetrahydrofuran-2-yl)methanesulfonamide (3h)
Eluated from the column with CH_2Cl_2 in 59 % yield as a white solid.
^{1}H NMR (400 MHz, $CDCl_3$): 7.46-7.44 (m, 2H), 7.42-7.27 (m, 3H), 6.03-6.00 (dd, *J* = 7.1, 6.0 Hz, 1H), 3.92-3.87 (m, 1H), 3.78-3.72 (m, 1H), 3.07 (s, 3H), 2.13-2.04 (m, 1H), 1.77-1.59 (m, 2H), 1.46-1.36 (m, 1H).
^{13}C NMR (101 MHz, $CDCl_3$): 136.2, 131.4, 129.3, 129.1, 89.5, 68.4, 39.8, 29.7, 24.8.
HRESI-MS: calculated for ($C_{11}H_{15}NO_3S$, M+H), 242.0851; found, 242.0853.



N-hexyl-4-methyl-N-(tetrahydrofuran-2-yl)benzenesulfonamide (3i)
Eluated from the column with hexane-EtOAc (9:1) in 67% yield as a colorless oil.
^{1}H NMR (400 MHz, $CDCl_3$): 7.78 (d, *J* = 8.3 Hz, 2H), 7.28 (d, *J* = 8.1, 2H), 5.80-5.76 (m, 1H), 3.91-3.85 (m, 1H), 3.76-3.71 (m, 1H), 3.02-2.88 (m, 2H), 2.41 (s, 3H), 2.17-2.11 (m, 1H), 1.95-1.76 (m, 4H), 1.61-1.50 (m, 1H), 1.32-1.19 (m, 6H), 0.88 (t, *J* = 6,7 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$): 143.2, 137.2, 129.5, 127.8, 88.8, 68.1, 43.4, 31.5, 31.5, 30.3, 26.9, 25.0, 22.7, 21.6, 14.1.
HRESI-MS: calculated for ($C_{17}H_{27}NO_3S$, M+Na), 348.1609; found, 348.1610.

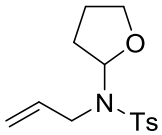


N-cyclohexyl-4-methyl-N-(tetrahydrofuran-2-yl)benzenesulfonamide (3j)
Eluated from the column with hexane-EtOAc (9:1) in 43% yield as a colorless oil.
^{1}H NMR (400 MHz, $CDCl_3$): 7.81 (d, *J* = 8.3 Hz, 2H), 7.25 (d, *J* = 8.6 Hz, 2H), 5.44-5.30 (m, 1H), 4.11-4.06 (m, 1H), 3.80-3.76 (m, 1H), 3.30-3.26 (m, 1H), 2.40 (s, 3H), 2.35-2.29 (m, 1H), 2.15-2.07 (m, 2H), 1.95-1.43 (m, 8H), 1.26-0.99 (m, 3H).
^{13}C NMR (101 MHz, $CDCl_3$): 142.8, 140.0, 129.4, 127.4, 88.8, 68.1, 57.7, 33.8, 31.4, 26.7, 25.5, 25.4, 21.6.
HRESI-MS: calculated for ($C_{17}H_{25}NO_3S$, M+H), 324.1633; found, 324.1639.

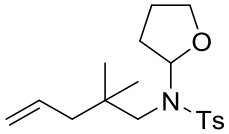


N-isopropyl-4-methyl-N-(tetrahydrofuran-2-yl)benzenesulfonamide (3k)
Isolated by gradient elution from the column with hexane-EtOAc (9:1 to 4:1) in 63 % yield as a colorless oil.
^{1}H NMR (400 MHz, $CDCl_3$): 7.72 (d, *J* = 8.3 Hz, 2H), 7.17 (d, *J* = 8.1 Hz, 2H), 5.30 (t, *J* = 7.0 Hz, 1H), 4.02-3.96 (m, 1H), 3.72-3.63 (m, 2H), 2.31 (s, 3H), 2.28-2.22 (m, 1H), 2.08-2.01 (m, 2H), 1.85-1.77 (m, 1H), 1.19 (d, *J* = 6.8 Hz, 3H), 1.00 (d, *J* = 6.8 Hz, 3H).

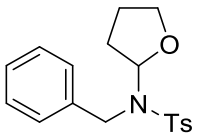
^{13}C NMR (101 MHz, $CDCl_3$): 142.8, 139.7, 129.4, 127.5, 88.3, 68.0, 49.1, 31.3, 25.4, 23.4, 21.6, 21.0.
HRESI-MS: calculated for ($C_{14}H_{21}NO_3S$, M+H), 284.1320; found 284.1316.



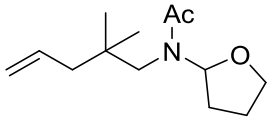
N-allyl-4-methyl-N-(tetrahydrofuran-2-yl)benzenesulfonamide (3l)
Eluated from the column with hexane-EtOAc (3:1) in 73 % yield as a colorless oil.
^{1}H NMR (400 MHz, $CDCl_3$): 7.78 (d, *J* = 8.2 Hz, 2H), 7.28 (d, *J* = 8.2 Hz, 2H), 5.93-5.84 (m, 2H), 5.23 (dd, *J* = 17.2, 1.2 Hz, 1H), 5.10 (dd, *J* = 10.0, 1.2 Hz, 1H), 3.90-3.84 (m, 1H), 3.76-3.67 (m, 3H), 2.42 (s, 3H), 2.16-2.08 (m, 1H), 2.00-1.85 (m, 3H).
^{13}C NMR (101 MHz, $CDCl_3$): 143.3, 137.1, 136.0, 129.5, 127.8, 116.4, 88.8, 68.3, 45.2, 30.0, 25.0, 21.6.
HRESI-MS: calculated for ($C_{14}H_{19}NO_3S$, M+H), 282.1164; found, 282.1166.



N-(2,2-dimethylpent-4-en-1-yl)-4-methyl-N-(tetrahydrofuran-2-yl)benzenesulfonamide (3m)
Isolated by gradient elution from the column with hexane-EtOAc (9:1 to 6:1) in 62% yield as a colorless oil.
^{1}H NMR (400 MHz, $CDCl_3$): 7.77 (d, *J* = 8.2 Hz, 2H), 7.28 (d, *J* = 8.2 Hz, 2H), 5.89-5.78 (m, 1H), 5.27-5.24 (m, 1H), 5.08-5.02 (m, 2H), 4.00-3.95 (m, 1H), 3.71-3.67 (m, 1H), 3.27 (d, *J* = 15.2 Hz, 1H), 2.83 (d, *J* = 15.2 Hz, 1H), 2.42 (s, 3H), 2.36-2.27 (m, 1H), 2.14-2.06 (m, 1H), 1.90-1.81 (m, 1H), 0.99 (s, 6H).
^{13}C NMR (101 MHz, $CDCl_3$): 143.1, 138.4, 135.1, 129.3, 127.90 117.7, 93.1, 68.0, 57.7, 45.9, 35.2, 31.3, 26.2, 25.8, 25.0, 21.6.
HRESI-MS: calculated for ($C_{18}H_{27}NO_3S$, M+Na), 360.1609; found, 360.1611

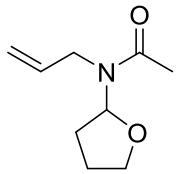


N-benzyl-4-methyl-N-(tetrahydrofuran-2-yl)benzenesulfonamide (3n)
Isolated by gradient elution from the column with hexane-EtOAc (9:1 to 4:1) in 61% yield as a white solid.
^{1}H NMR (400 MHz, $CDCl_3$): 7.81 (d, *J* = 8.2 Hz, 2H), 7.43 (d, *J* = 7.5 Hz, 2H), 7.35-7.27 (m, 5 H), 5.95-5.92 (m , 1H), 4.44 (d, *J* = 17.0 Hz, 1H), 4.15 (d, *J* = 17.0 Hz, 1H), 3.91-3.86 (m, 1H), 3.78-3.73 (m, 1H), 2.44 (s, 3H), 2.03-1.97 (m, 1H), 1.95-1.64 (m, 3H).
^{13}C NMR (101 MHz, $CDCl_3$): 143.4, 138.5, 136.9, 129.5, 128.5, 127.8, 127.2, 127.1, 88.9, 68.5, 46.0, 30.2, 24.8, 21.6.
HRESI-MS: calculated for ($C_{18}H_{21}NO_3S$, M+H), 332.1320; found, 332.1311

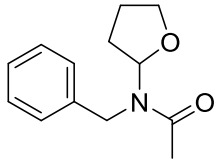


N-(2,2-dimethylpent-4-en-1-yl)-N-(tetrahydrofuran-2-yl)acetamide (5a)

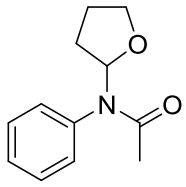
Eluated from the column with hexane-EtOAc (5:1) in 54 % yield as a pale yellow oil.
^{1}H NMR (400 MHz, CD_2Cl_2): 5.91-5.80 (m, 1H), 5.35 (br, 1H), 5.03-4.99 (m, 2H), 3.98 (m, 1H), 3.74-3.69 (m, 1H), 3.38 (d, *J* = 13.5 Hz, 1H), 3.04 (d, *J* = 13.5 Hz, 1H), 2.13-1.92 (m, 9H), 0.87 (s, 6H)
^{13}C NMR (101 MHz, CD_2Cl_2): 172.5, 136.1, 117.1, 90.7, 67.3, 52.7, 46.3, 36.0, 30.1, 26.0, 25.8, 25.4, 23.2.
HRESI-MS: calculated for ($C_{13}H_{23}NO_2$, M+H), 226.1807; found 226.1811.



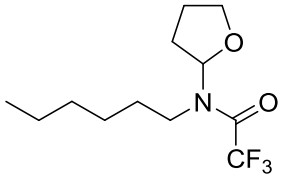
N-allyl-N-(tetrahydrofuran-2-yl)acetamide (5b)
Isolated by gradient elution from the column with hexane-EtOAc (9:1 to 6:1) in 82% as a colorless oil.
^{1}H NMR (400 MHz, DMSO-d6, 373K): 5.87-5.73 (m, 2H), 5.12 (dd, *J* = 17.4, 1.4 Hz, 1H), 5.07 (dd, *J* = 10.4, 1.4 Hz, 1H), 3.93-3.84 (m, 3H), 3.71-3.67 (m, 1H), 2.07-2.02 (m, 4H), 1.98-1.82 (m, 3H).
^{13}C NMR (101 MHz, DMSO-d6, 373K): 170.2, 135.5, 114.3, 86.1, 66.4, 43.3, 28.3, 24.1, 21.0.
HRESI-MS: calculated for ($C_9H_{15}NO_2$, M+Na), 192.1001; found 192.1008.



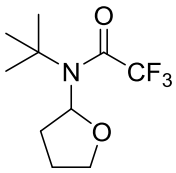
N-benzyl-N-(tetrahydrofuran-2-yl)acetamide (5c)
Eluated from the column with hexane-EtOAc (4:1) in 71 % yield as an off-white solid.
^{1}H NMR (400 MHz, DMSO-d6, 373K): 7.30-7.21 (m, 5H), 5.84 (m, 1H), 4.58 (d, *J* = 16.7 Hz, 1H), 4.40 (d, *J* = 16.7 Hz, 1H), 3.90-3.85 (m, 1H), 3.72-3.67 (m, 1H), 2.08-2.01 (m, 4H), 1.91-1.73 (m, 3H).
^{13}C NMR (101 MHz, DMSO-d6, 373K): 170.1, 138.9, 127.4, 126.7, 125.8, 86.6, 66.4, 44.4, 28.5, 24.1, 21.2.
HRESI-MS: calculated for ($C_{13}H_{17}NO_2$, M+H), 220.1338; found 220.1341.



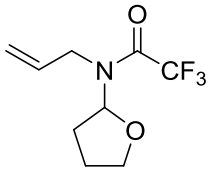
N-phenyl-N-(tetrahydrofuran-2-yl)acetamide (5d)
Isolated by gradient elution from the column with hexane-EtOAc (4:1 to 2:1) in 95 % yield as a white solid
^{1}H NMR (400 MHz, CD_2Cl_2): 7.43-7.20 (m, 5H), 6.45 (br, 1H), 3.63-3.60 (m, 2H), 2.03-1.98 (m, 1H), 1.72-1.62 (m, 5H), 1.25-1.22 (m, 1H).
^{13}C NMR (101 MHz, CD_2Cl_2): 171.1, 139.5, 131.0, 129.5, 128.6, 84.4, 68.4, 29.5, 25.3, 23.6.
HRESI-MS: calculated for ($C_{12}H_{15}NO_2$, M+H), 206.1181; found 206.1177.



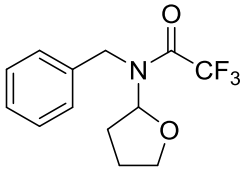
2,2,2-trifluoro-N-hexyl-N-(tetrahydrofuran-2-yl)acetamide (5e)
Isolated by gradient elution from the column with hexane-EtOAc (20:1 to 10:1) in 62% yield as a colorless oil.
^{1}H NMR (400 MHz, DMSO-d6, 373K): 5.63-5.60 (m, 1H) 4.05-3.99 (m, 1H), 3.82-3.77 (m, 1H), 3.41-3.34 (m, 1H), 3.26-3.19 (m, 1H), 2.25-2.20 (m, 1H), 2.03-1.92 (m, 3H), 1.68-1.52 (m, 2H), 1.35-1.29 (m, 6H), 0.89 (t, *J* = 6.5 Hz, 3H).
^{13}C NMR (101 MHz, DMSO-d6, 373K): 155.1 (q, *J* = 35 Hz), 115.7 (q, *J* = 289 Hz), 87.0, 67.7, 42.3, 30.0, 29.2, 27.5, 25.4, 24.0, 21.1, 12.7.
HRESI-MS: calculated for ($C_{12}H_{20}F_3NO_2$, M+Na), 290.1344; found, 290.1348.



N-(tert-butyl)-2,2,2-trifluoro-N-(tetrahydrofuran-2-yl)acetamide (5f)
Eluated from the column with hexane-EtOAc (5:1) in 58% yield as a colorless oil.
^{1}H NMR (400 MHz, CD_2Cl_2): 5.40 (m, 1H), 4.06-4.01 (m, 1H), 3.71-3.65 (m, 1H), 2.20-2.08 (m, 3H), 1.99-1.93 (m, 1H), 1.49 (s, 9H)
^{13}C NMR (101 MHz, CD_2Cl_2): 159.1 (q, *J* = 37 Hz), 117.0 (q, *J* = 290 Hz), 88.9, 67.0, 60.2, 31.1, 28.8, 24.7.
HRESI-MS: calculated for ($C_{10}H_{16}F_3NO_2$, M+Na), 262.1031; found, 262.1035.

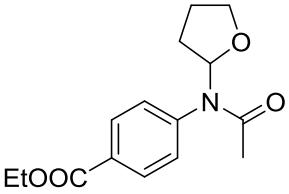


N-allyl-2,2,2-trifluoro-N-(tetrahydrofuran-2-yl)acetamide (5g)
Eluated from the column with hexane-EtOAc (9:1) in 80 % yield as a yellowish oil.
^{1}H NMR (400 MHz, DMSO-d6, 373K): 5.90-5.81 (m, 1H), 5.70-5.67 (m, 1H), 5.22-5.13 (m, 2H), 4.05-3.99 (m, 3H), 3.82-3.77 (m, 1H), 2.26-2.18 (m, 1H), 2.08-1.90 (m, 3H)
^{13}C NMR (101 MHz, DMSO-d6, 373K): 155.3 (q, *J* = 35 Hz), 133.3, 115.7, 115.6 (q, *J* = 290 Hz), 86.8, 67.7, 43.9, 29.0, 23.9.
HRESI-MS: calculated for ($C_9H_{12}F_3NO_2$, M+Na), 246.0718; found, 246.0720.

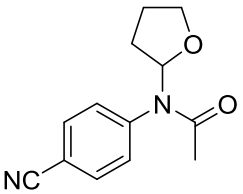


N-benzyl-2,2,2-trifluoro-N-(tetrahydrofuran-2-yl)acetamide (5h)
Isolated by gradient elution from the column with hexane-EtOAc (3:1 to 2:1) in 89 % yield as slightly yellowish oil.

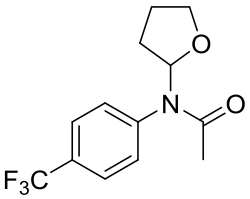
^{1}H NMR (400 MHz, CD_2Cl_2): 7.25-7.15 (m, 5H), 5.70 (m, 1H), 4.54 (d, *J* = 15.7 Hz, 1H), 4.38 (d, *J* = 15.8 Hz, 1H), 3.97-3.91 (m, 1H), 3.77-3.72 (m, 1H), 2.11-2.03 (m, 1H), 1.91-1.72 (m, 3H).
^{13}C NMR (101 MHz, CD_2Cl_2): 157.2 (q, *J* = 36 Hz), 137.5, 128.9, 127.6, 127.1, 117.0 (q, *J* = 289 Hz), 87.9, 69.2, 45.9, 30.5, 25.7.
HRESI-MS: calculated for ($C_{13}H_{14}F_3NO_2$, M+Na), 296.0874; found, 296.0873.



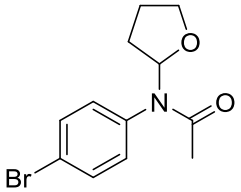
Ethyl-4-(N-(tetrahydrofuran-2-yl)acetamido)benzoate (5i)
Eluated from the column with hexane-EtOAc (3:1) in 93 % yield as a colorless oil.
^{1}H NMR (400 MHz, CD_2Cl_2): 8.07 (d, *J* = 8.5 Hz, 2H), 7.38-7.27 (br, 2H), 6.48-6.36 (br, 1H), 4.37 (q, *J* = 7.1 Hz, 2H), 3.65-3.61 (m, 2H), 2.08-2.00 (m, 1H), 1.78-1.58 (br+m, 5H), 1.38 (t, *J* = 7.1 H, 3H), 1.30-1.23 (m, 1H).
^{13}C NMR (101 MHz, CD_2Cl_2) δ 170.7, 166.1, 143.7, 131.0, 130.7, 118.8, 85.1, 68.5, 61.6, 29.7, 25.3, 23.63, 14.5.
HRESI-MS: calculated for ($C_{15}H_{19}NO_4$, M+Na), 300.1212; found 300.1206.



N-(4-cyanophenyl)-N-(tetrahydrofuran-2-yl)acetamide (5j)
Isolated by gradient elution from the column with hexane-EtOAc (4:1 to 3:2) in 89 % yield as a colorless oil.
^{1}H NMR (400 MHz, CD_3CN): 7.79 (d, *J* = 7.4 Hz, 2H), 7.43 (d, *J* = 7.6 Hz, 2H), 6.27 (br, 1H), 3.61 (m, 2H), 2.08-1.99 (m, 1H), 1.76-1.54 (m, 5H), 1.27-1.18 (m, 1H).
^{13}C NMR (101 MHz, CD_3CN): 171.5, 144.26, 134.1, 132.5, 119.1, 112.7, 85.9, 68.7, 29.9, 25.4, 23.5.
HRESI-MS: calculated for ($C_{13}H_{14}N_2O_2$, M+Na), 253.0953; found 253.0956.



N-(tetrahydrofuran-2-yl)-N-(4-(trifluoromethyl)phenyl)acetamide (5k)
Eluated from the column with hexane-EtOAc (7:3) in 95 % yield as a colorless oil.
^{1}H NMR (400 MHz, CD_2Cl_2): 7.69 (d, *J* = 8.1 Hz, 2H), 7.48-7.35 (br, 2H), 6.51-6.32 (br, 1H), 3.68-3.63 (m, 2H), 2.10-2.00 (m, 1H), 1.87-1.55 (m, 5H), 1.33-1.23 (m, 1H).
^{13}C NMR (101 MHz, CD_2Cl_2): 170.7, 143.0, 131.6, 130.6 (q, *J* = 32 Hz), 126.7, 124.4 (q, *J* = 273 Hz), 84.9, 68.4, 29.6, 25.3, 23.6.
HRESI-MS: calculated for ($C_{13}H_{14}F_3NO_2$, M+Na), 296.0874; found 296.0865.



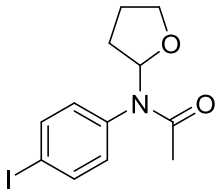
N-(4-bromophenyl)-N-(tetrahydrofuran-2-yl)acetamide (5l)

Isolated by gradient elution from the column with hexane-EtOAc (4:1 to 2:1) in 95 % yield as a white solid

^{1}H NMR (400 MHz, CD_2Cl_2): 7.55 (d, *J* = 8.2 Hz, 2H), 7.30-6.99 (br, 2H), 6.42 (br, 1H), 3.66-3,60 (m, 2H), 2.07-1.98 (m, 1H), 1.82-1.57 (m, 5H), 1.34-1.24 (m, 1H).

^{13}C NMR (101 MHz, CD_2Cl_2): 170.8, 138.6, 132.7, 122.6, 84.4, 68.4, 29.6, 25.3, 23.7.

HRESI-MS: calculated for ($C_{12}H_{14}BrNO_2$, M+Na), 306.0106; found 306.0117.



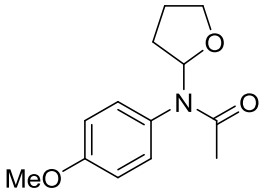
N-(4-iodophenyl)-N-(tetrahydrofuran-2-yl)acetamide (5m)

Isolated by gradient elution from the column with hexane-EtOAc (4:1 to 2:1) in 90 % yield as a white solid

^{1}H NMR (400 MHz, CD_3CN): 7.78 (d, *J* = 8.2 Hz, 2H), 7.07-7.03 (br, 2H), 6.42-6.32 (br, 1H), 3.60-3.54 (m, 2H), 2.03-1.94 (m, 1H), 1.77-1.56 (m, 1H), 1.26-1.20 (m, 1H).

^{13}C NMR (101 MHz, CD_3CN): 171.0, 140.0, 139.3, 133.8, 94.3, 84.8, 68.7, 29.9, 25.5, 23.6.

HRESI-MS: calculated for ($C_{12}H_{14}INO_2$, M+H), 332.0148; found 332.0164.



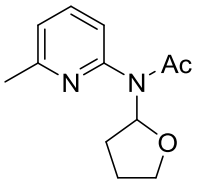
N-(4-methoxyphenyl)-N-(tetrahydrofuran-2-yl)acetamide (5n)

Eluated from the column with hexane-EtOAc (4:1) in 93 % yield as a beige solid.

^{1}H NMR (400 MHz, CD_2Cl_2): 7.26 (br, 1H), 7.05 (br, 1H), 6.91 (d, *J* = 8.24 Hz, 2H), 6.38 (m, 1H), 3.82 (s, 3H), 3.67-3.63 (m, 2H), 2.05-1.95 (m, 1H), 1.76-1.63 (m, 5H), 1.31-1.24 (m, 1H)

^{13}C NMR (101 MHz, CD_2Cl_2): 172.5, 159.8, 131.9, 122.0, 114.6, 84.6, 68.5, 55.8, 29.4, 25.3, 23.6.

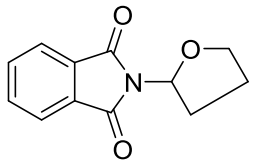
HRESI-MS: calculated for ($C_{13}H_{17}NO_3$, M+H), 236.1287; found 236.1278.



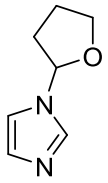
N-(6-methylpyridin-2-yl)-N-(tetrahydrofuran-2-yl)acetamide (5o)

Isolated by gradient elution from the column with hexane-EtOAc (10:1 to 2:1) in 86 % yield as a colorless oil.

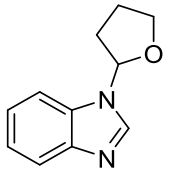
^{1}H NMR (400 MHz, CD_2Cl_2): 7.69 (t, *J* = 7.7 Hz, 1H), 7.20 (d, *J* = 7.6 Hz, 1H), 7.11 (d, *J* = 7.7 Hz, 1H), 6.31-6.28 (m, 1H), 3.74-3.65 (m, 2H), 2.53 (s, 3H), 2.08-2.00 (m, 1H), 1.80-1.66 (m, 5H), 1.37-1.25 (m, 1H).
^{13}C NMR (101 MHz, CD_2Cl_2): 171.9, 159.4, 152.3, 139.0, 123.4, 122.1, 85.7, 68.6, 29.3, 25.1, 24.3, 23.5.
HRESI-MS: calculated for ($C_{12}H_{16}N_2O_2$, M+H), 221.1290; found 221.1292.



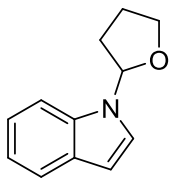
2-(tetrahydrofuran-2-yl)isoindoline-1,3-dione (5p)
Isolated by gradient elution from the column with hexane-EtOAc (9:1 to 6:1) in 75% yield as a white solid.
^{1}H NMR (400 MHz, $CDCl_3$): 7.86 (m, 2H), 7.73 (m, 2H), 6.06-6.03 (m, 1H), 4.23-4.16 (m, 1H), 3.96-3.93 (m, 1H), 2.57-2.50 (m, 1H), 2.42-2.24 (m, 2H), 2.04-1.98 (m, 1H).
^{13}C NMR (101 MHz, $CDCl_3$): 168.0, 134.3, 132.0, 123.5, 81.0, 67.0, 29.3, 26.2.
HRESI-MS: calculated for ($C_{12}H_{11}NO_4$, M+H), 218.0817; found, 218.0812



1-(Tetrahydrofuran-2-yl)-1*H*-imidazole (7a)
Isolated by flash column chromatography (methanol/ dichloromethane = 1:10) in 52% as colorless oil. ^{1}H and ^{13}C NMR spectra of the compound correspond to that published before.[6]

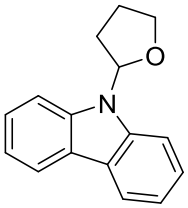


1-(Tetrahydrofuran-2-yl)-1*H*-benzo[d]imidazole (7b)
Isolated by flash column chromatography (methanol/ dichloromethane = 1:10) in 85% yield as colorless oil. ^{1}H and ^{13}C NMR spectra of the product correspond to that published before.[6]

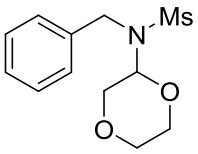


N-[Tetrahydrofuran-2-yl]-1H-indole (7c)
Isolated by gradient elution from the column with hexane-EtOAc (20:1 to 9:1) in 57% yield as a colorless liquid.
^{1}H NMR (400 MHz, CD_2Cl_2): 7.59 (d, *J* = 7.7 Hz, 1H), 7.46 (d, *J* = 8.2 Hz, 1H),7.25 – 7.18 (m, 2H), 7.12 (dd, *J* = 7.6, 7.6 Hz, 1H), 6.51 (d, *J* = 3.0 Hz, 1H), 6.22 (dd, *J* = 5.7, 4.2 Hz, 1H), 4.13-4.07 (m, 1H), 4.00-3.94 (m, 1H), 2.47-2.37 (m, 2H), 2.23-2.08 (m, H-2H).

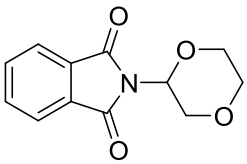
^{13}C NMR (101 MHz, CD_2Cl_2): 136.1, 129.5, 124.5, 122.0, 121.1, 120.2, 110.4, 102.4, 86.2, 68.7, 31.9, 25.2.
GCMS: [M] =187 detected which corresponds to $C_{12}H_{13}NO$; the purity was further confirmed by GCMS.



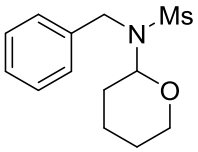
9-(tetrahydrofuran-2-yl)-9H-carbazole (7d)
Isolated by gradient elution from the column with hexane-EtOAc (15:1 to 9:1) in 65% yield as a white solid
^{1}H NMR (400 MHz, $CDCl_3$): 8.10 (d, *J* = 8.48 Hz, 2H), 7.54-7.39 (m, 4H), 7.29-7.24 (m, 2H), 6.52-6.49 (m, 1H), 4.44-4.39 (m, 1H), 4.10-4.06 (m, 1H), 2.56-2.47 (m, 1H), 2.42-2.20 (m, 3H).
^{13}C NMR (101 MHz, $CDCl_3$): 139.1, 125.8, 123.9, 120.4, 119.7, 110.5, 86.6, 68.2, 29.5, 25.8.
HRESI-MS: calculated for ($C_{16}H_{15}NO$, M+H), 238.1232; found, 238.1241



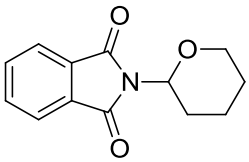
N-benzyl-N-(1,4-dioxan-2-yl)methanesulfonamide (8a)
Isolated by gradient elution from the column with hexane-EtOAc (6:1 to 4:1) in 47 % yield as a beige solid.
^{1}H NMR (400 MHz, CD_2Cl_2): 7.39-7.24 (m, 5H), 5.20-5.17 (m, 1H), 4.54 (d, *J* = 16.6 Hz, 1H), 4.43 (d, *J* = 16.6 Hz, 1H), 3.87-3.83 (m, 2H), 3.61-3.58 (m, 1H), 3.48-3.40 (m, 2H), 3.26-3.21 (m, 1H), 2.97 (s, 3H).
^{13}C NMR (101 MHz, CD_2Cl_2): 138.6, 128.9, 127.8, 127.6, 83.4, 69.3, 67.3, 66.0, 47.8, 40.3.
HRESI-MS: calculated for ($C_{12}H_{17}NO_4S$, M+Na), 294.0776; found 294.0779.



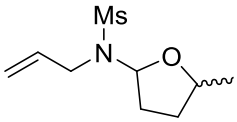
2-(1,4-dioxan-2-yl)isoindoline-1,3-dione (8b)
Isolated by gradient elution from the column with hexane-EtOAc (9:1 to 4:1) in 85% yield as a white solid.
^{1}H NMR (400 MHz, $CDCl_3$): 7.87 (m, 2H), 7.76 (m, 2H), 5.56-5-53 (m, 1H), 4.61-4.56 (m, 1H), 3,98-3.95 (m, 2H), 3.78-3-76 (m, 3H).
^{13}C NMR (101 MHz, $CDCl_3$): 167.2, 134.6, 131.7, 123.8, 76.3, 67.7, 66.5, 65.8.
HRESI-MS: calculated for ($C_{12}H_{11}NO_4$, M+H), 234.0766; found, 234.0768.



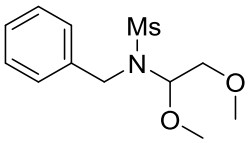
N-benzyl-N-(tetrahydro-2H-pyran-2-yl)methanesulfonamide (8c)
Isolated by gradient elution from the column with hexane-EtOAc (9:1 to 6:1) in 68 % yield as a white solid.
^{1}H NMR (400 MHz, CD_2Cl_2): 7.39-7.24 (m, 5H), 5.03-5.01 (m, 1H), 4.53-4.40 (m, 2H), 4.01-3.98 (m, 1H), 3.59-3.53 (m, 1H), 2.93 (s, 3H), 1.79-1.76 (m, 1H), 1.56-1.36 (m, 5H)
^{13}C NMR (101 MHz, CD_2Cl_2): 139.4, 128.7, 127.4, 127.4, 86.8, 68.4, 47.1, 40.0, 31.4, 25.4, 23.9.
HRESI-MS: calculated for ($C_{13}H_{19}NO_3S$, M+Na), 292.0983; found 292.0977.



2-(tetrahydro-2H-pyran-2-yl)isoindoline-1,3-dione 31 (8d)
Isolated by gradient elution from the column with hexane-EtOAc (9:1 to 6:1) in 43 % yield as a white solid.
^{1}H NMR (400 MHz, CD_2Cl_2): 7.85 (m, 2 H), 7.74 (m, 2H), 5.30-5.26 (m, 1H), 4.06-4.03 (m, 1H), 3.65-3.59 (m, 1H), 2.76-2.66 (m, 1H), 2.02-1.98 (m, 1H), 1.71-1.52 (m, 4H).
^{13}C NMR (101 MHz, CD_2Cl_2): 167.7, 134.6, 132.2, 123.7, 79.6, 69.2, 28.2, 25.4, 24.0.
HRESI-MS: calculated for ($C_{13}H_{13}NO_3$, M+H), 232.0974; found 232.0963.

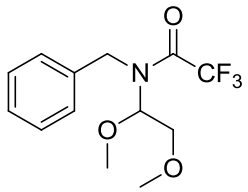


N-allyl-N-(5-methyltetrahydrofuran-2-yl)methanesulfonamide (8e)
Isolated by gradient elution from the column with hexane-EtOAc (20:1 to 10:1) in 61 % yield as a colorless oil. The ratio of two diastereomers is 2:3.
^{1}H NMR (400 MHz, CD_2Cl_2): 6.00-5.89 (m, $1H_{overlap}$), [5.68-5.65 (m, $0.6H_{mayor}$), 5.57-5.54 (m, $0.4H_{minor}$)], 5.30 (m, $1H_{overlap}$), 5.16 (m, $1H_{overlap}$), [4.26-4.20 (m, $0.6H_{mayor}$), 3.97-3.92 (m, $0.4H_{minor}$)], 3.85-3.73 (m, $2H_{overlap}$) 2.90 (s. $3H_{overlap}$), 2.16-1.92 (m, $3H_{overlap}$), 1.53-1.41 (m, $1H_{overlap}$), [1.26 (d, J = 6.0 Hz, $1.2H_{minor}$), 1.18 (d, J = 6.0 Hz, $1.8H_{mayor}$).]
^{13}C NMR (101 MHz, CD_2Cl_2): 136.3, 136.1, 116.8, 116.7, 88.8, 88.6, 76.7, 75.1, 45.8, 45.7, 39.9, 39.8, 33.2, 32.0, 30.9, 29.8, 21.7, 21.00
HRESI-MS: calculated for ($C_9H_{17}NO_3S$, M+Na), 242.0827; found 242.0818.

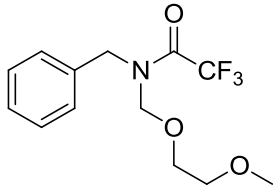


N-benzyl-N-(1,2-dimethoxyethyl)methanesulfonamide (8f)
Isolated by gradient elution from the column with hexane-EtOAc (9:1 to 4:1) in 50 % yield as a colorless oil
^{1}H NMR (400 MHz, CD_2Cl_2): 7.43-7.28 (m, 5H), 5.11-5.08 (m, 1H), 4.43 (d, J = 15.8 Hz, 1H), 4.29 (d, J = 15.8 Hz, 1H), 3.47 (m, 2H), 3.32 (s, 3H), 3.25 (s, 3H), 2.77 (s, 3H).
^{13}C NMR (101 MHz, CD_2Cl_2): 138.1, 129.0, 128.7, 127.8, 87.8, 71.8, 59.0, 55.9, 46.0, 41.9.

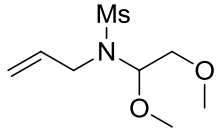
HRESI-MS: calculated for ($C_{12}H_{19}NO_4S$, M+Na), 296.0933; found 296.0942.



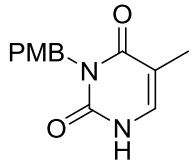
N-benzyl-N-(1,2-dimethoxyethyl)-2,2,2-trifluoroacetamide (8g)
Isolated by gradient elution from the column with hexane-EtOAc (10:1 to 5:1) in 41 % yield as a colorless oil.
^{1}H NMR (400 MHz, CD_2Cl_2): 7.32-7.26 (m, 5H), 5.16 (m, 1H), 4.68 (d, *J* = 15.3 Hz, 1H), 4.53 (d, *J* = 15.3 Hz, 1H), 3.47-3.40 (m, 1H), 3.34-3.28 (m, 4H), 3.17 (s, 3H).
^{13}C NMR (101 MHz, CD_2Cl_2): 156.7 (q, *J* = 33 Hz), 137.3, 128.7, 128.2, 119.7 (q, *J* = 289 Hz), 87.3, 72.1, 59.1, 56.2, 44.7.
HRESI-MS: calculated for ($C_{13}H_{16}F_3NO_3$, M+Na), 314.0980; found 314.0975.



N-benzyl-2,2,2-trifluoro-N-((2-methoxyethoxy)methyl)acetamide (8g')
Isolated by gradient elution from the column with hexane-EtOAc (10:1 to 5:1) in 20 % yield as a colorless oil.
^{1}H NMR (400 MHz, CD_2Cl_2): 7.39-7.23 (m, 5H), 4.81 (d, *J* = 14.9 Hz, 2H), 4.70 (s, 2H), 3.62-3.50 (m, 2H), 3.48 (m, 2H), 3.33 (s, 3H)
^{13}C NMR (101 MHz, CD_2Cl_2): 157.3 (q, *J* = 34 Hz), 135.9, 129.1, 128.8, 128.3, 116.8 (q, *J* = 287 Hz), 77.0, 72.0, 68.0, 59.1, 48.5.
HRESI-MS: calculated for ($C_{13}H_{16}F_3NO_3$, M+Na), 314.0980; found 314.0974.

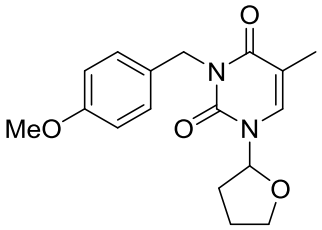


N-allyl-N-(1,2-dimethoxyethyl)methanesulfonamide (8h)
Eluated from the column with hexane-EtOAc (7:3) in 56 % yield as a colorless oil
^{1}H NMR (400 MHz, CD_2Cl_2): 5.90-5.81 (m, 1H), 5.28 (dd, *J* = 17.2 Hz, 1.5 Hz, 1H), 5.17 (dd, *J* = 10.2 Hz, 1.3 Hz, 1H), 5.03 (m, 1H), 3.83 (d, *J* = 6.28 Hz, 2H), 3.49-3.39 (m, 2H), 3.34 (s, 3H), 3.30 (s, 3H), 2.91 (s, 3H).
^{13}C NMR (101 MHz, CD_2Cl_2): 135.5, 118.1, 87.3, 71.8, 59.0, 55.5, 44.4, 42.5.
HRESI-MS: calculated for ($C_8H_{17}NO_4S$, M+Na), 246.0776; found 246.0780.

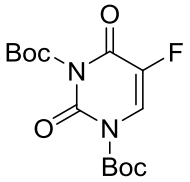


3-(4-methoxybenzyl)-5-methylpyrimidine-2,4(1H,3H)-dione (9a)
^{1}H NMR (400 MHz, $CDCl_3$): 9.59 (br, 1H), 7.43 (d, *J* = 8.3 Hz, 2H), 6.99 (d, *J* = 5.2 Hz, 1H), 6.83 (d, *J* = 8.3 Hz, 2H), 5.05 (s, 2H), 3.77 (s, 3H), 1.92 (s, 3H).

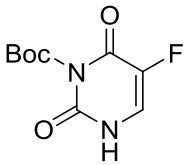
^{13}C NMR (101 MHz, $CDCl_3$): 164.1, 159.2, 153.1, 134.3, 130.7, 129.1, 113.8, 110.5, 55.4, 43.5, 13.2.
HRESI-MS: calculated for ($C_{13}H_{14}N_2O_3$, M+H), 247.1083; found 247.1088.



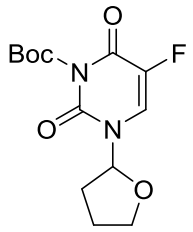
3-(4-methoxybenzyl)-5-methyl-1-(tetrahydrofuran-2-yl)pyrimidine-2,4(1H,3H)-dione (10a)
Isolated by gradient elution from the column with hexane-EtOAc (10:1 to 4:1) in 85 % yield as white solid.
^{1}H NMR (101 MHz, CD_2Cl_2): 7.36 (d, *J* = 8.5 Hz, 2H), 7.11 (s, 1H), 6.81 (d, *J* = 8.5 Hz, 2H), 6.01 (dd, *J* = 6.1, 2.9 Hz, 1H), 5.04-4.96 (m, 2H), 4.20-4.15 (m, 1H), 3.95-3.90 (m, 1H), 3.75 (s, 3H), 2.39-2.29 (m, 1H), 2.03-1.90 (m, 6H).
^{13}C NMR (101 MHz, CD_2Cl_2): 163.8, 159.4, 151.2, 133.6, 130.6, 129.9, 113.8, 109.7, 87.7, 70.3, 55.6, 43.9, 33.0, 24.5, 13.5.
HRESI-MS: calculated for ($C_{17}H_{20}N_2O_4$, M+H), 317.1501; found 317.1509.



di-tert-butyl 5-fluoro-2,4-dioxopyrimidine-1,3(2H,4H)-dicarboxylate (9b')
Recrystallized from hexane-EtOAc (10:1) in 68 % yield
^{1}H NMR (400 MHz, $CDCl_3$): 7.97 (d, *J* = 6.44 Hz, 1H), 1.60 (s, 18H)
^{13}C NMR (101 MHz, $CDCl_3$): 154.5 (d, *J* = 28.8 Hz), 147.5, 146.1, 144.2, 139.9 (d, *J* = 243.4 Hz), 123.4 (d, *J* = 37.0 Hz), 88.4, 88.2, 27.9, 27.5.
HRESI-MS: calculated for ($C_{14}H_{19}FN_2O_6$, M+Na), 353.1125; found 353.1130.



tert-butyl 5-fluoro-2,6-dioxo-3,6-dihydropyrimidine-1(2H)-carboxylate (9b)
Isolated by flash cromatography on silica gel (eluent - hexane-EtOAc 3:2) in 40% yield
^{1}H NMR (400 MHz, DMSO-d6): 11.53 (s, 1H), 7.98 (d, *J* = 6.04 Hz, 1H), 1.51 (s, 9H).
^{13}C NMR (101 MHz, DMSO-d6): 155.1 (d, *J* = 28.0 Hz), 147.5, 147.1, 139.1 (d, *J* = 229.3 Hz), 127.4 (d, *J* = 38.0 Hz), 86.6, 27.0.
HRESI-MS: calculated for ($C_9H_{11}FN_2O_4$, M+Na), 253.0601; found 253.0611.



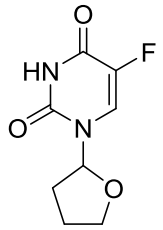
tert-butyl-5-fluoro-2,6-dioxo-3-(tetrahydrofuran-2-yl)-3,6-dihydropyrimidine-1(2H)-carboxylate (10b)

Isolated by gradient elution from the column with hexane-EtOAc (10:1 to 5:2) in 81 % yield as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): 7.42 (d, *J* = 6.12 Hz, 1H), 5.97-5.95 (m, 1H), 4.27-4.22 (m, 1H), 4.04-3.98 (m, 1H), 2.47-2.37 (m, 1H), 2.18-2.05 (m, 2H), 1.97-1.90 (m, 1H), 1.62 (s, 9H)

^{13}C NMR (101 MHz, $CDCl_3$): 154.8 (d, *J* = 28.0 Hz), 146.8, 146.7, 139.9 (d, *J* = 238.0 Hz), 123.2 (d, *J* = 34.2 Hz), 88.2, 87.8, 70.6, 33.1, 27.5, 23.8.

HRESI-MS: calculated for ($C_{13}H_{17}FN_2O_5$, M+Na), 323.1019; found 323.1012.

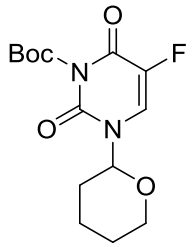


5-fluoro-1-(tetrahydrofuran-2-yl)pyrimidine-2,4(1H,3H)-dione (Tegafur)

N3-Boc-N1-tetrahydrofuranyl-5-fluorouracil (**10b)** (60 mg, 0.2 mmol) was heated to 75˚C in 2 mL of isopropanol for 4h. The evaporation of the solvent under reduced pressure gave 5-fluoro-1-(tetrahydro-2-furyl)-2,4(1H,3H)-pyrimidinedione in quantative yield (40 mg).

^{1}H NMR (400 MHz, DMSO-d6): 11.77 (br, 1H), 7.87 (d, *J* = 6.96 Hz, 1H), 5.90-5.88 (m, 1H), 4.24-4.19 (m, 1H), 3.81-3.75 (m, 1H), 2.25-2.17 (m, 1H), 2.03-1.87 (m, 3H)

^{13}C NMR (101 MHz, DMSO-d6): 157.2 (d, *J* = 26.3 Hz), 148.9, 139.9 (d, *J* = 231.0 Hz), 125.0 (d, *J* = 34.0 Hz), 86.3, 69.3, 31.5, 23.7.

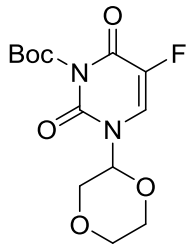


tert-butyl 5-fluoro-2,6-dioxo-3-(tetrahydro-2H-pyran-2-yl)-3,6-dihydropyrimidine-1(2H)-carboxylate (10c)

^{1}H NMR (400 MHz, $CDCl_3$): 7.50 (d, *J* = 6.1 Hz, 1H), 5.55-5.51 (m, 1H), 4.16-4.12 (m, 1H), 3.69-3.62 (m, 1H), 2.02-1.94 (m, 2H), 1.63-1.57 (m, 2H), 1.61 (s, 9H), 1.51-1.41 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): 154.6 (d, *J* = 28 Hz), 146.9, 146.7, 140.2 (d, *J* = 239 Hz), 123.8 (d, *J* = 34 Hz), 87.8, 83.1, 69.4, 31.2, 27.6, 24.9, 22.6.

HRESI-MS: calculated for ($C_{13}H_{17}FN_2O_6$, M+Na), 337.1176; found 337.1171.

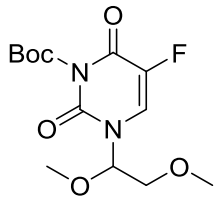


tert-butyl 3-(1,4-dioxan-2-yl)-5-fluoro-2,6-dioxo-3,6-dihydropyrimidine-1(2H)-carboxylate (10d)

^{1}H NMR (400 MHz, $CDCl_3$): 7.64 (d, *J* = 6.0 Hz, 1H), 5.72-5.70 (m, 1H), 4.03-3.99 (m, 2H), 3.95-3.90 (m, 1H), 3.81-3.77 (m, 1H), 3.70-3.63 (m, 1H), 3.43-3.38 (m, 1H), 1.60 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): 154.4 (d, *J* = 28 Hz), 146.9, 146.4, 140.1 (d, *J* = 238 Hz), 123.9 (d, *J* = 35 Hz), 88.1, 78.9, 68.2, 66.8, 65.8, 27.5.

HRESI-MS: calculated for ($C_{13}H_{17}FN_2O_6$, M+Na), 339.0968; found 339.0978.



tert-butyl 3-(1,2-dimethoxyethyl)-5-fluoro-2,6-dioxo-3,6-dihydropyrimidine-1(2H)-carboxylate (10e)

Isolated by gradient elution from the column with hexane/EtOAc as eluent (10:1) in 44 % yield as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): 7.47 (d, *J* = 5.8 Hz, 1H), 5.69-5.67 (m, 1H), 3.60-3.58 (m, 2H), 3.42 (s, 3H), 3.40 (s, 3H), 1.62 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): 154.7 (d, *J* = 27 Hz), 147.9, 146.7, 140.3 (d, *J* = 240 Hz), 123.7 (d, *J* = 33.5 Hz), 88.0, 85.4, 72.4, 59.9, 57.6, 27.6.

HRESI-MS: calculated for ($C_{13}H_{19}FN_2O_6$, M+Na), 341.1125; found 341.1120.

8. References

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[3] Barluenga, J.; Álvarez-Gutiérrez, J. M.; Ballesteros, A.; González, J. M., *Angew. Chem. Int. E.*, **2007**, *46*, 1281 –1283.

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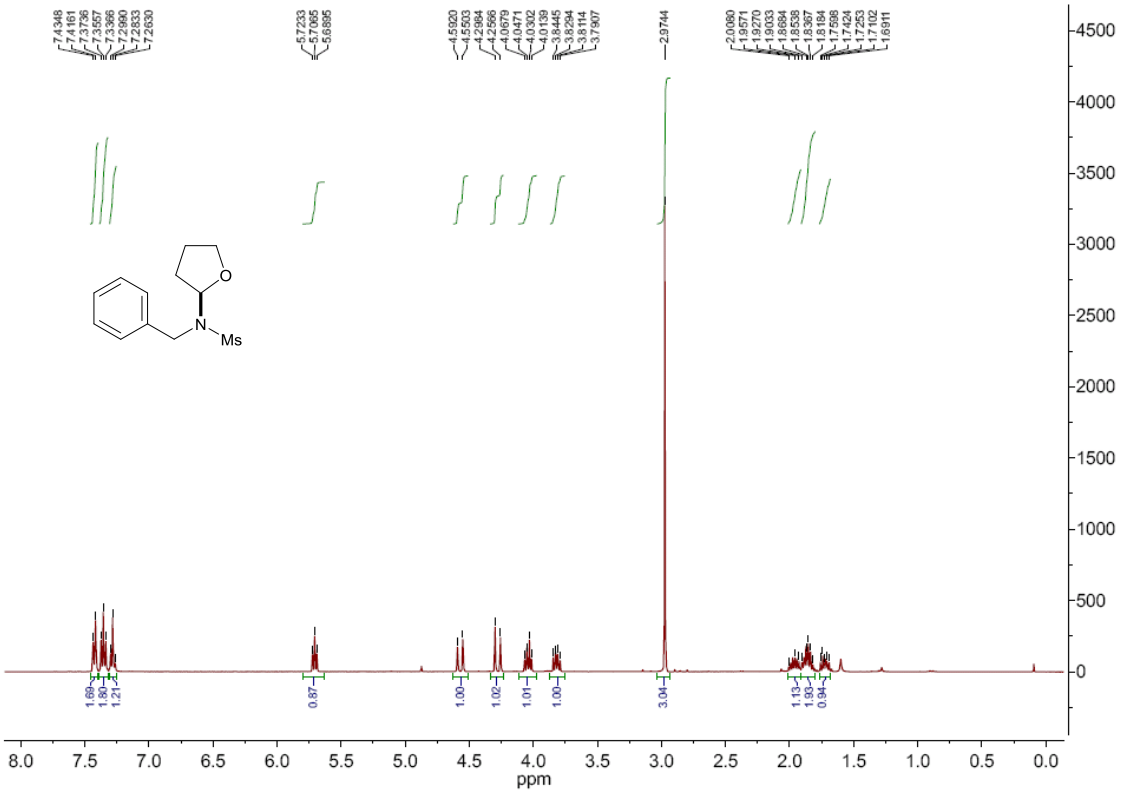
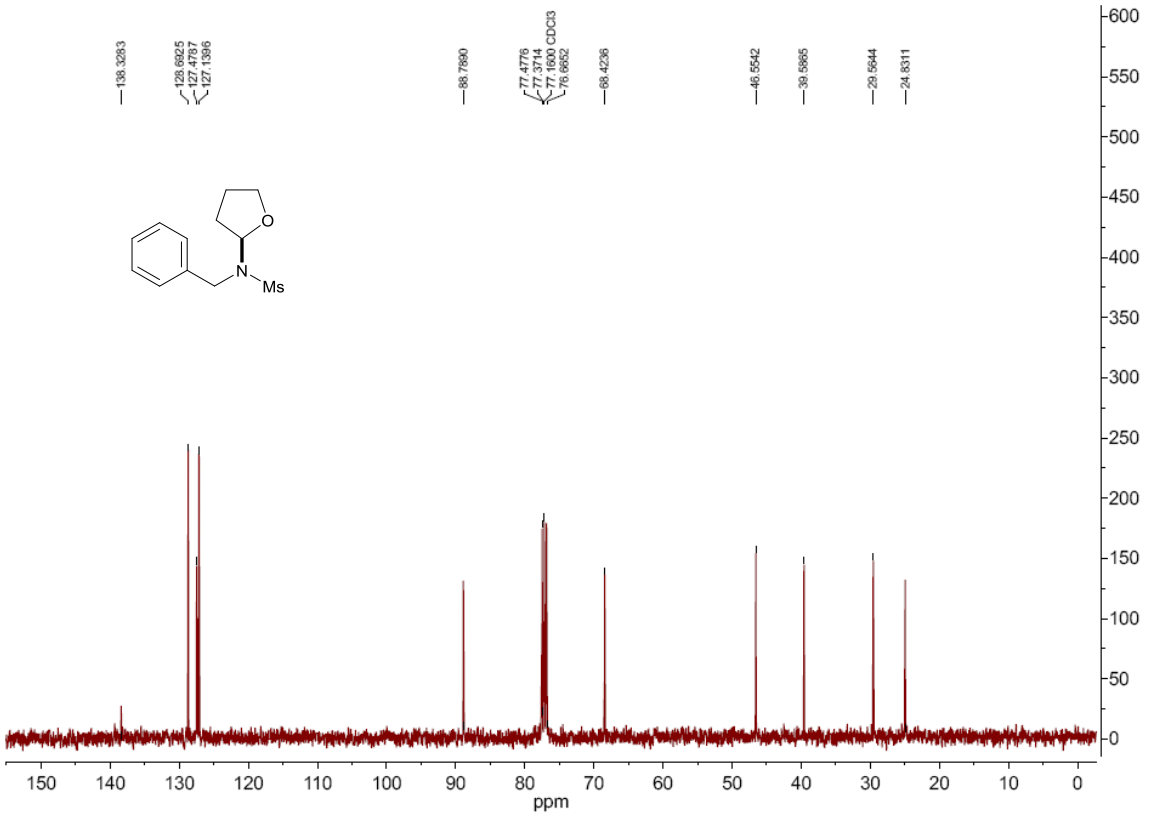
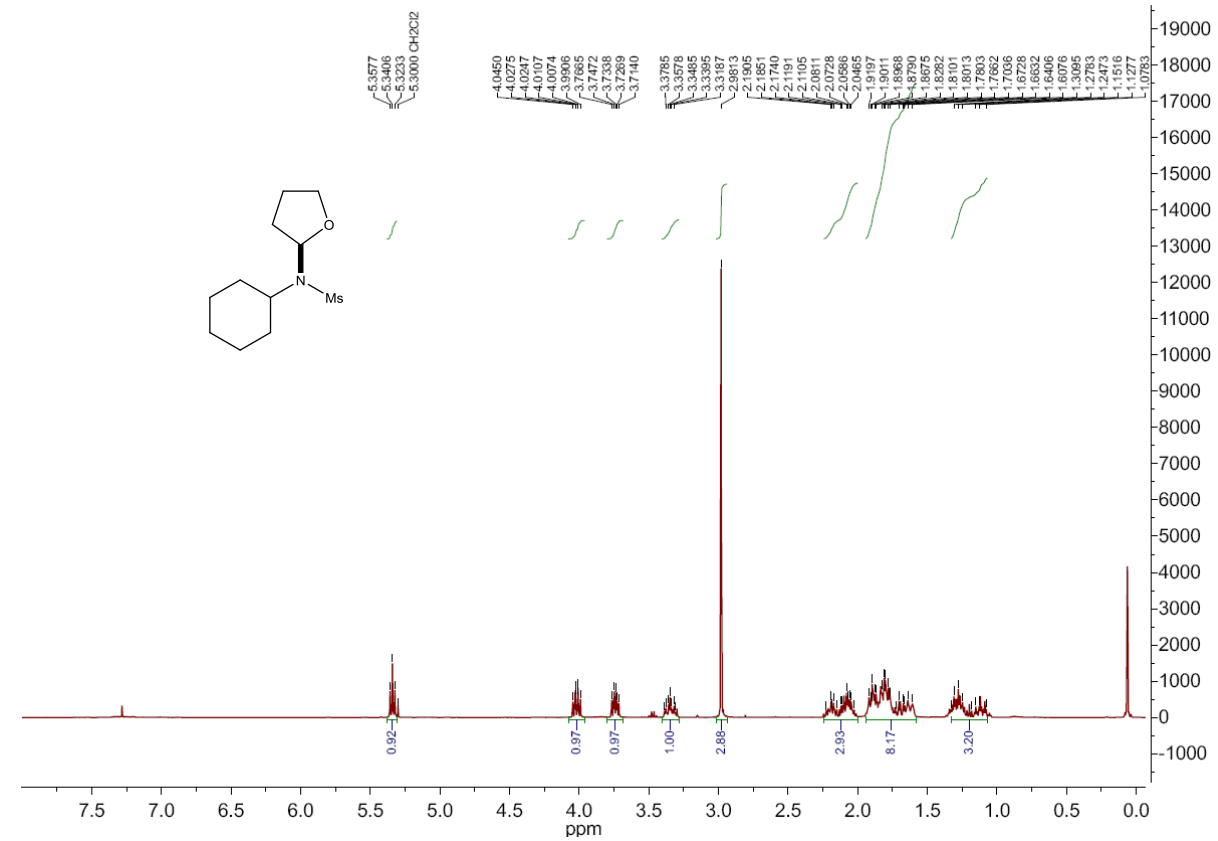
9. NMR Spectra

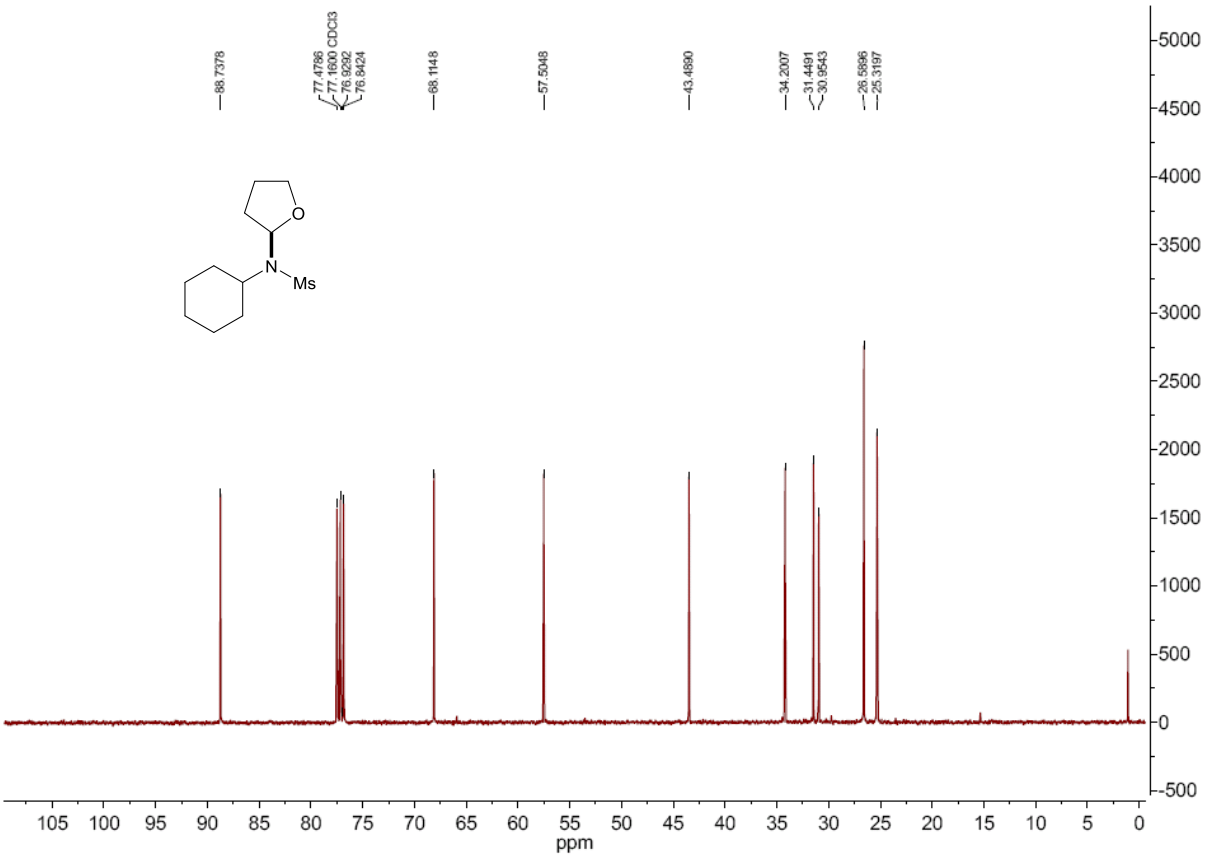
^{1}H and ^{13}C NMR spectra of N-benzyl-N-(tetrahydrofuran-2-yl)methanesulfonamide (3a)



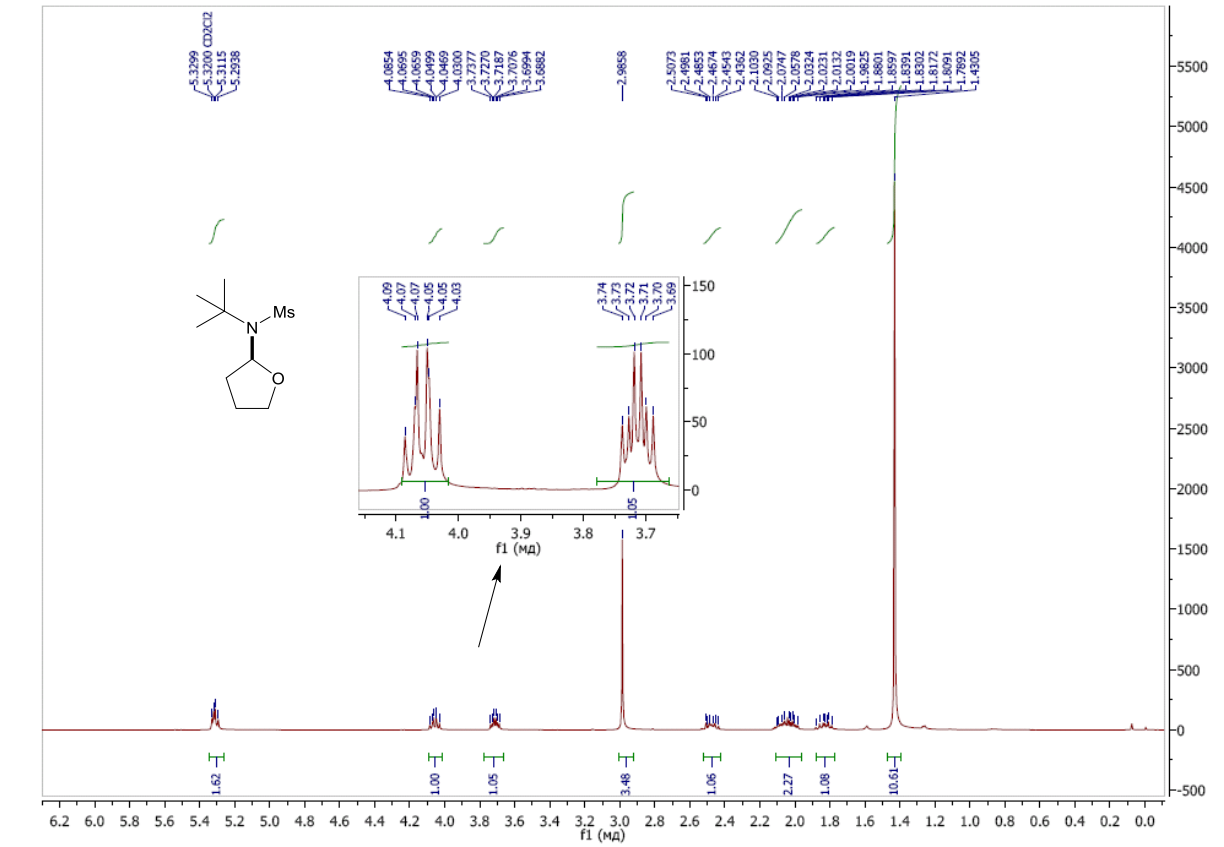


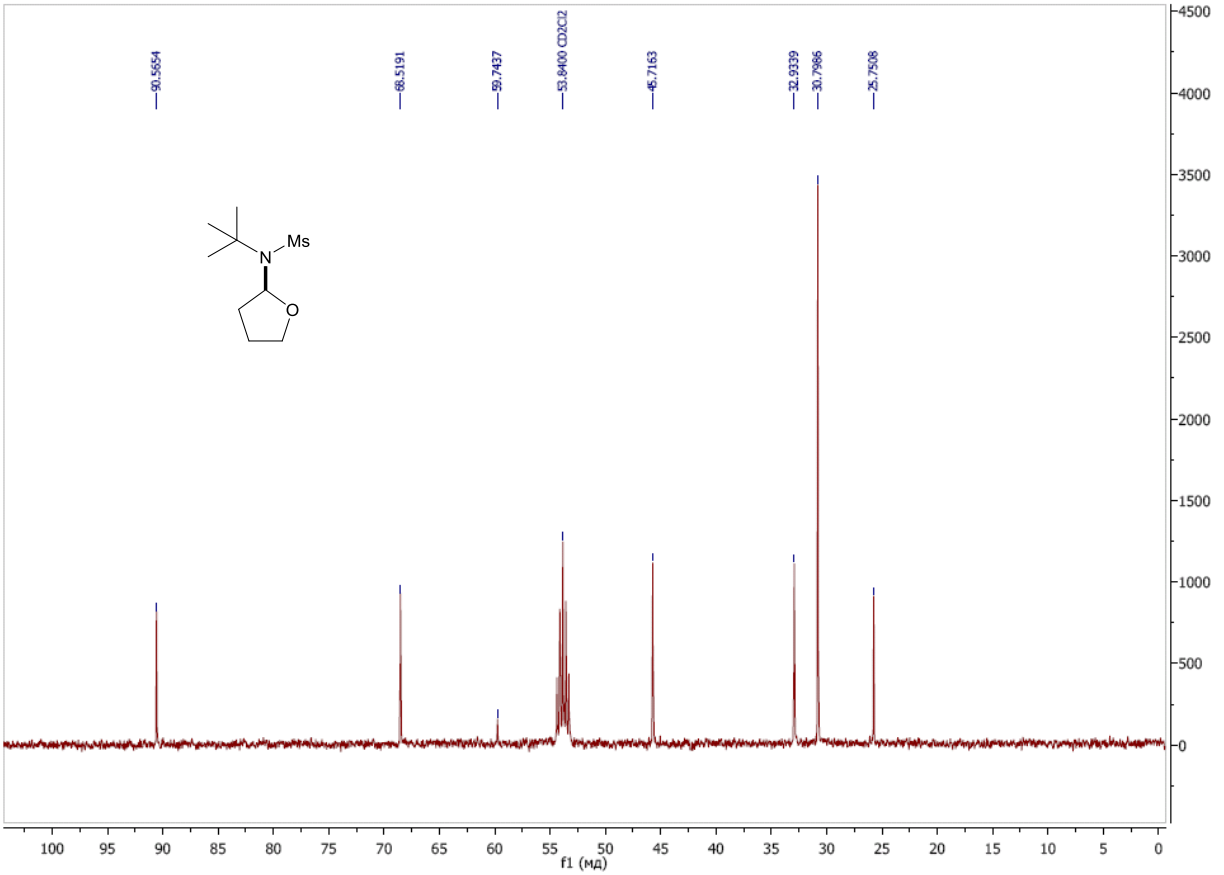
^{1}H and ^{13}C NMR spectra of N-cyclohexyl-N-(tetrahydrofuran-2-yl)methanesulfonamide (3b)



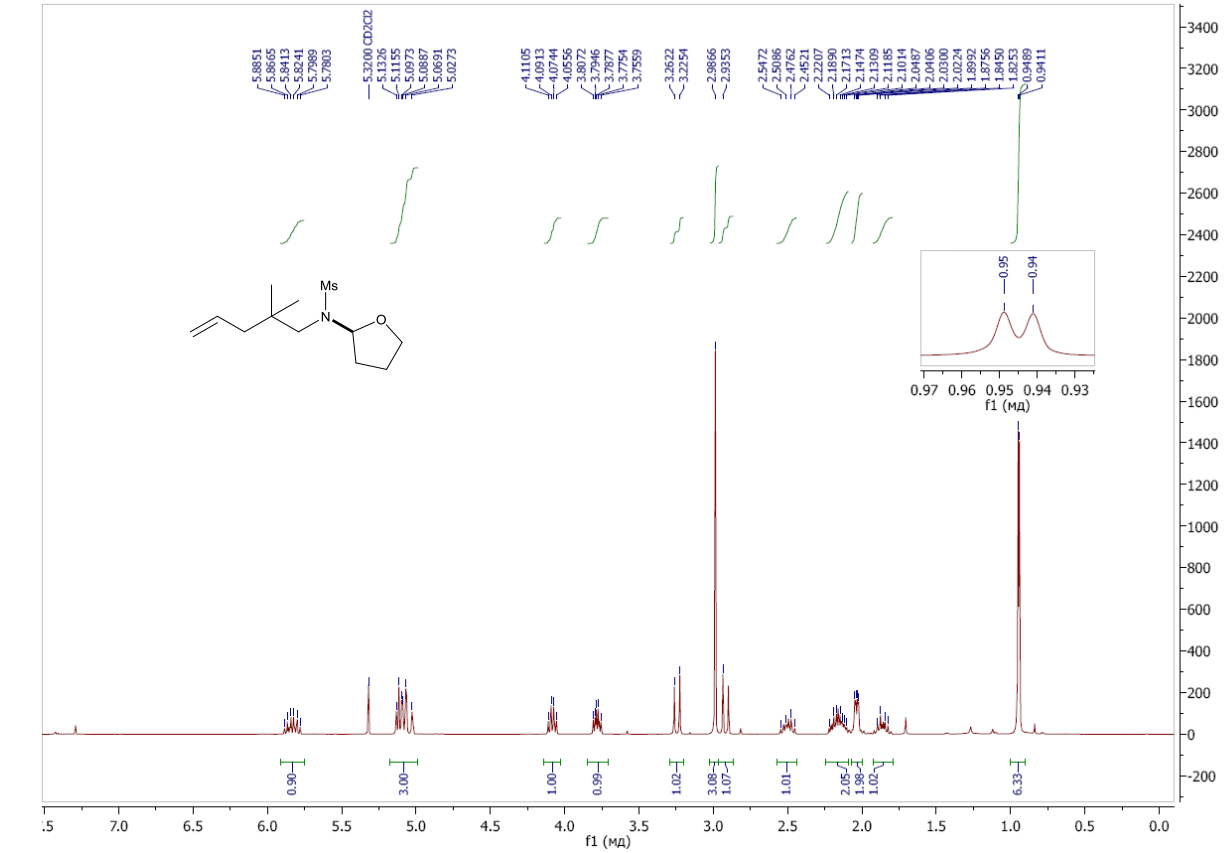


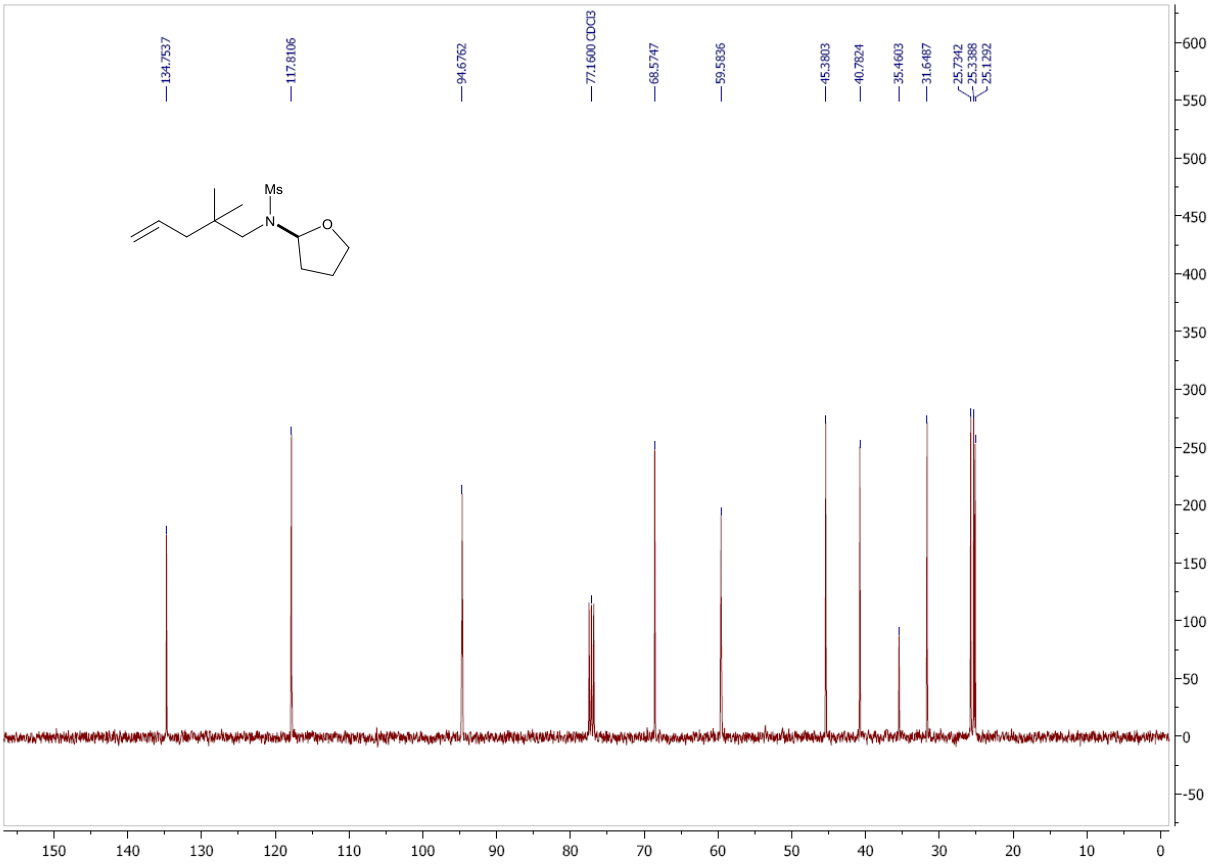
^{1}H and ^{13}C NMR spectra of N-(tert-butyl)-N-(tetrahydrofuran-2-yl)methanesulfonamide (3c)



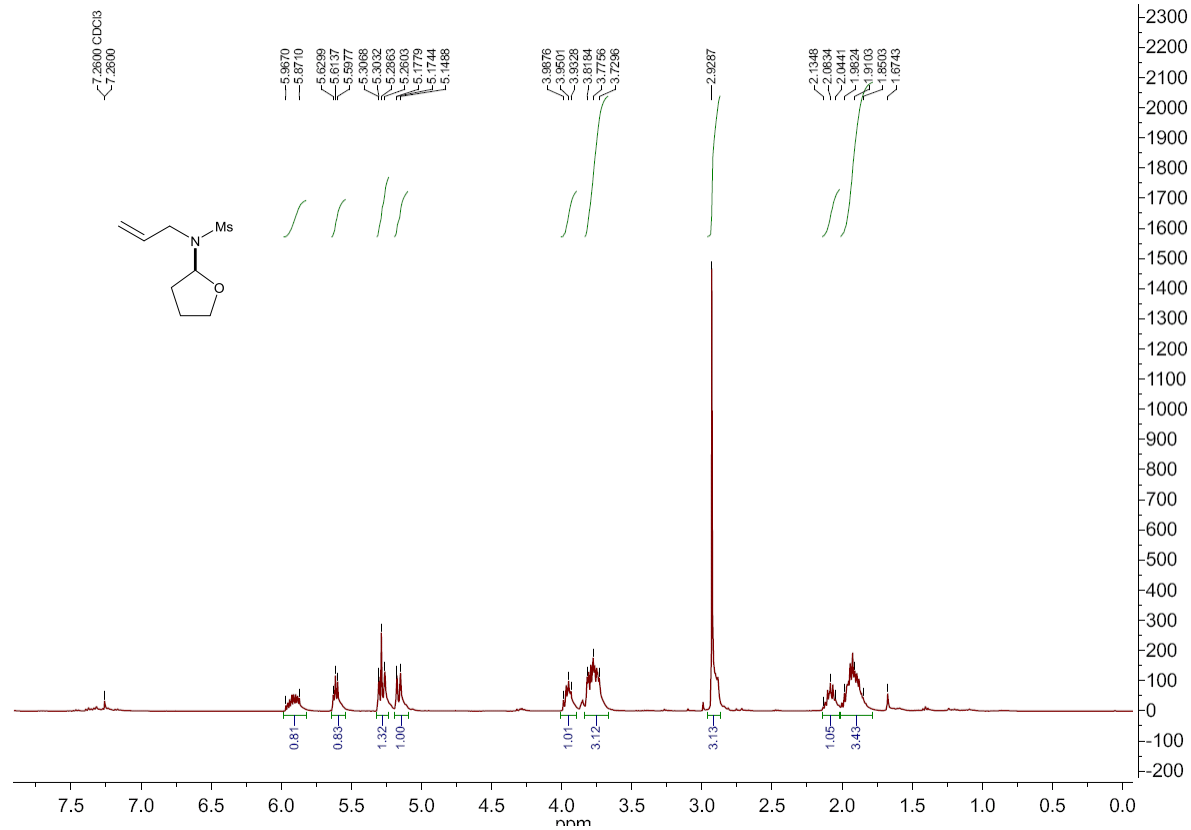


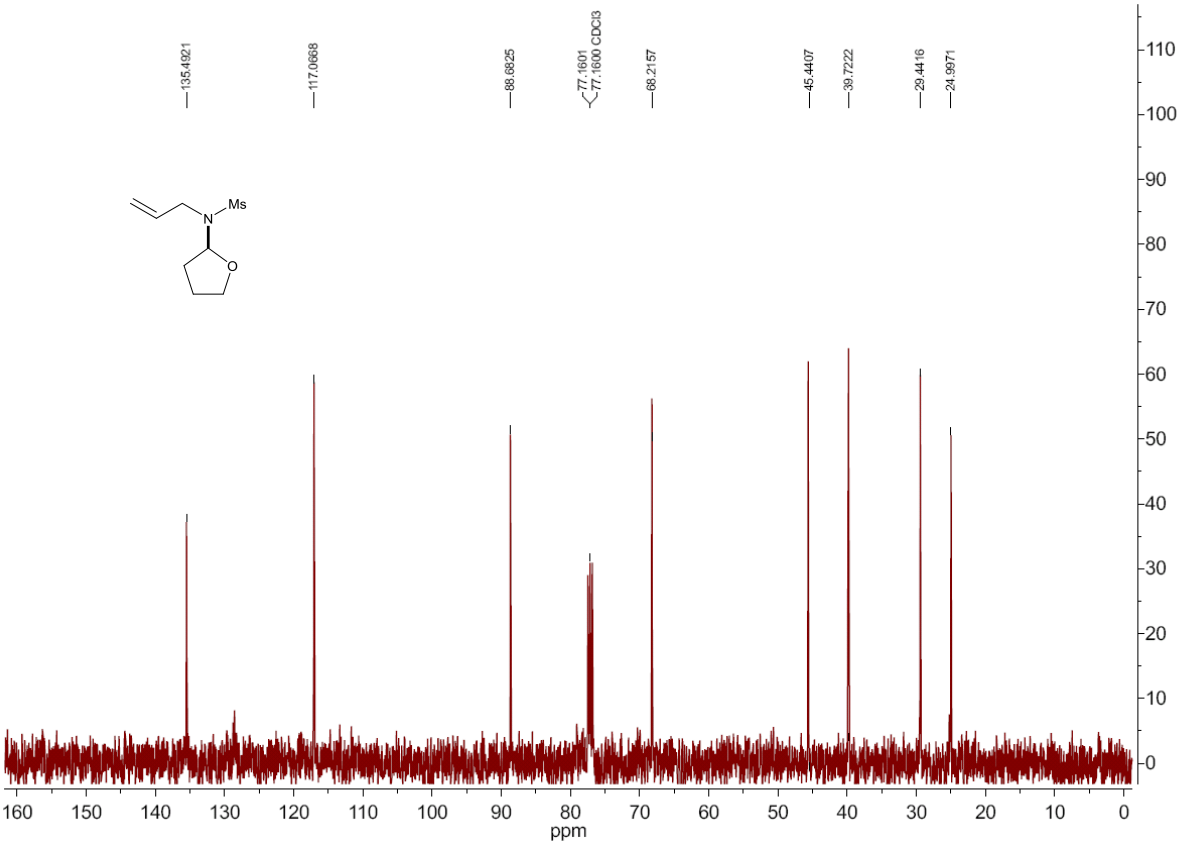
^{1}H and ^{13}C NMR of N-(2,2-dimethylpent-4-en-1-yl)-N-(tetrahydrofuran-2-yl)methanesulfonamide (3d)



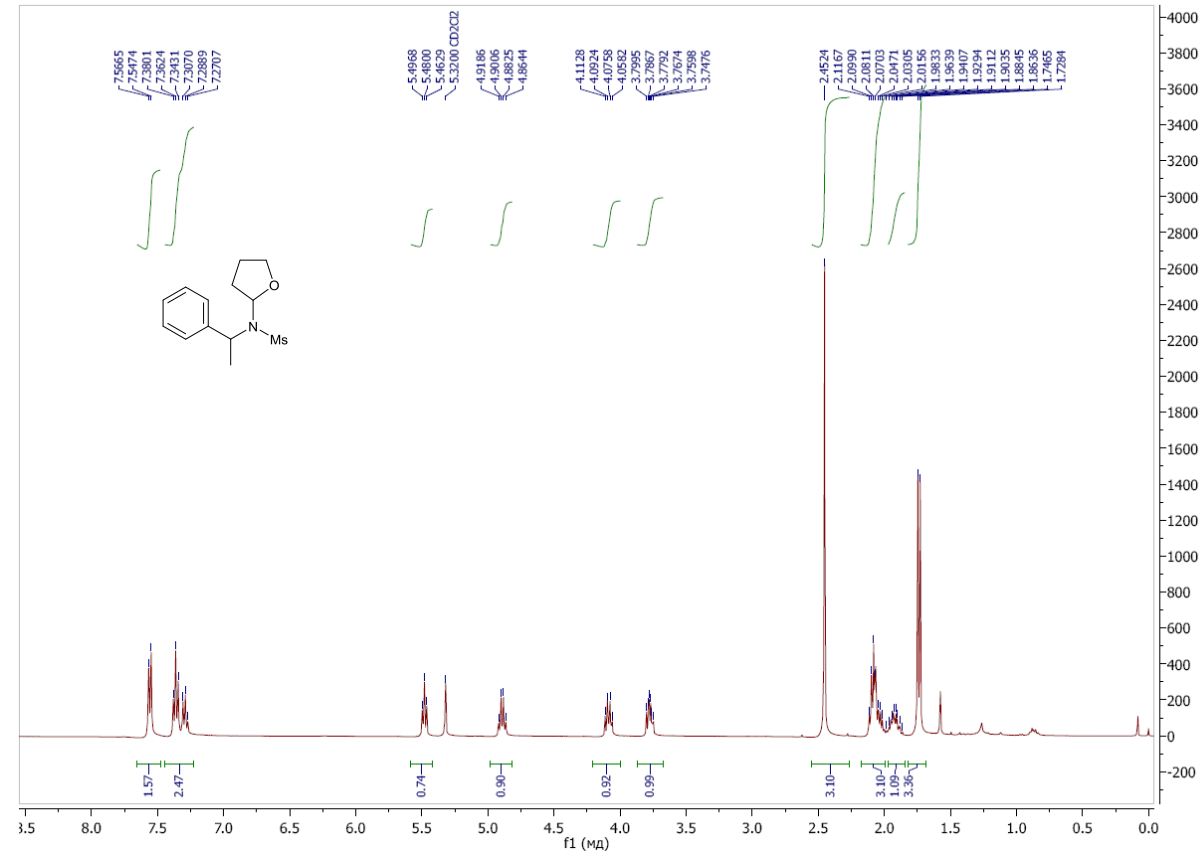


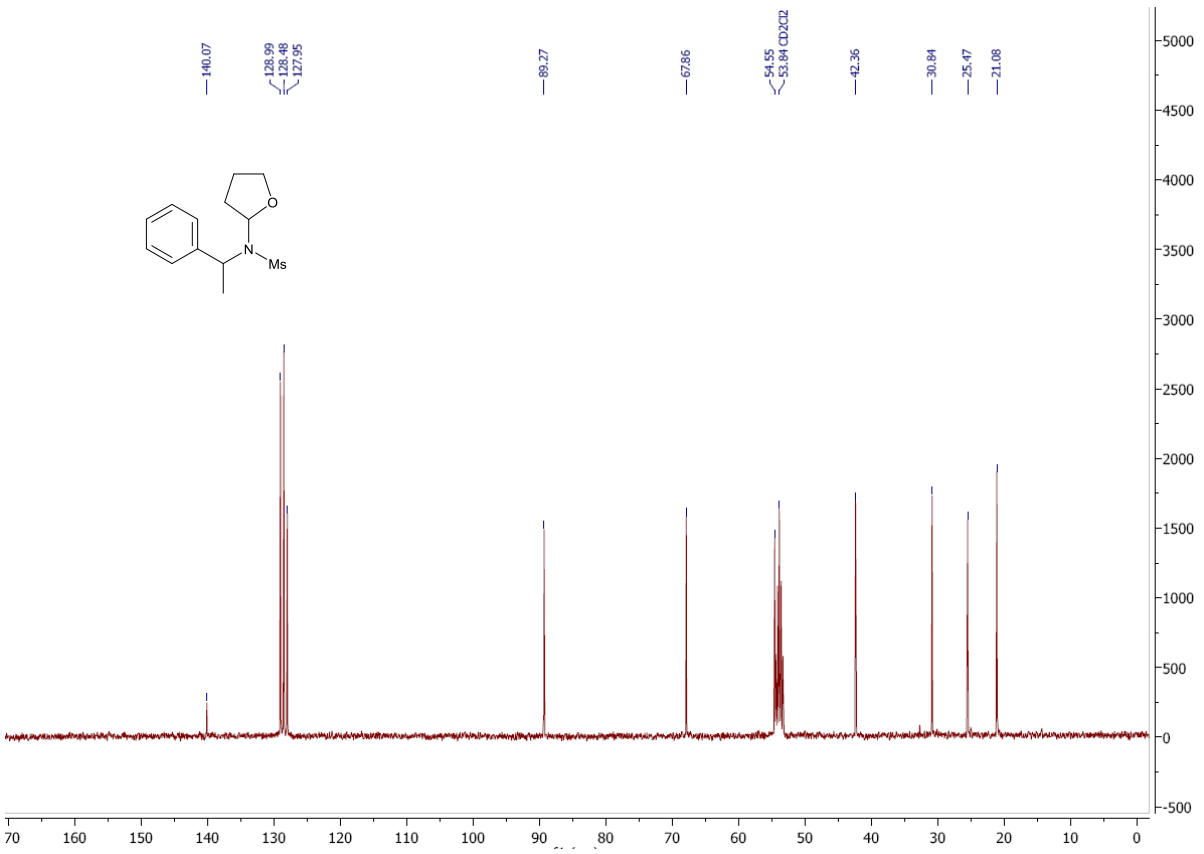
^{1}H and ^{13}C NMR of N-allyl-N-(tetrahydrofuran-2-yl)methanesulfonamide (3e)



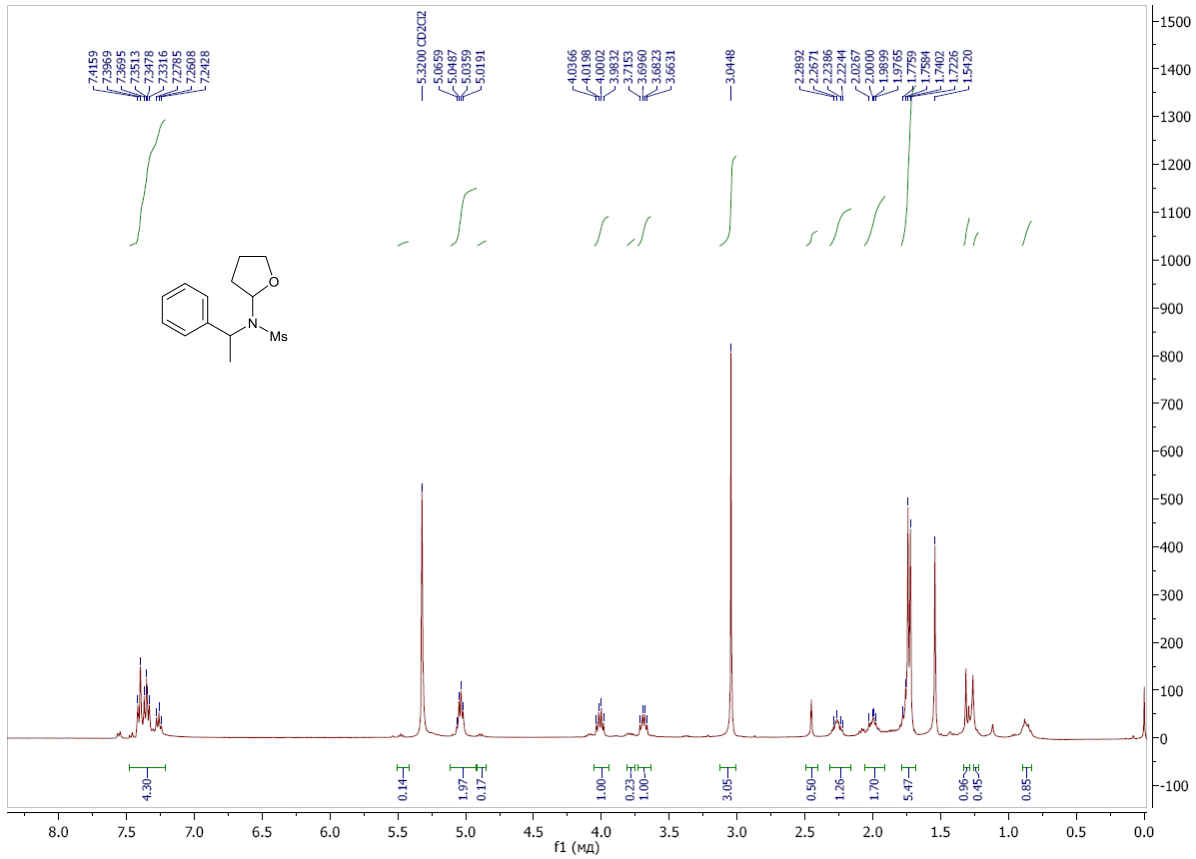


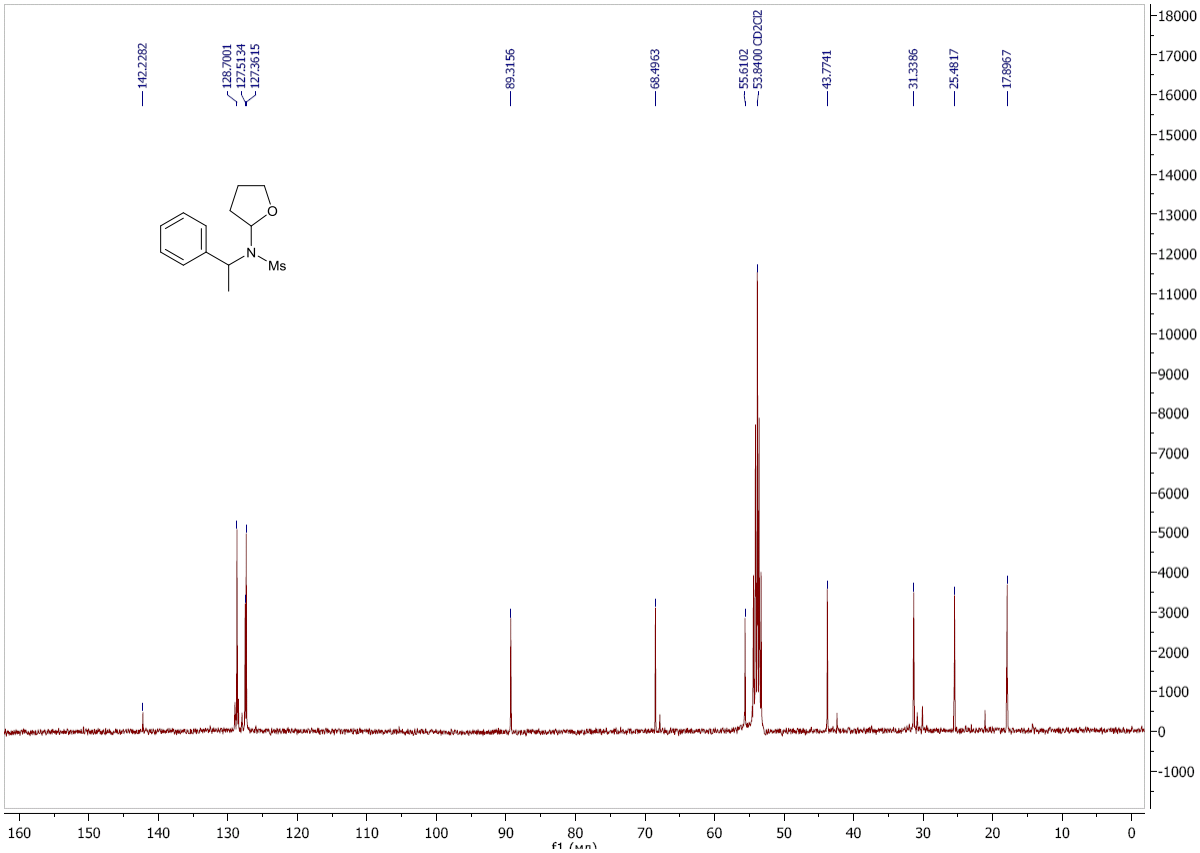
^{1}H and ^{13}C NMR of N-(1-phenylethyl)-N-(tetrahydrofuran-2-yl)methanesulfonamide (d.r. 2:3) major isomer (3f)



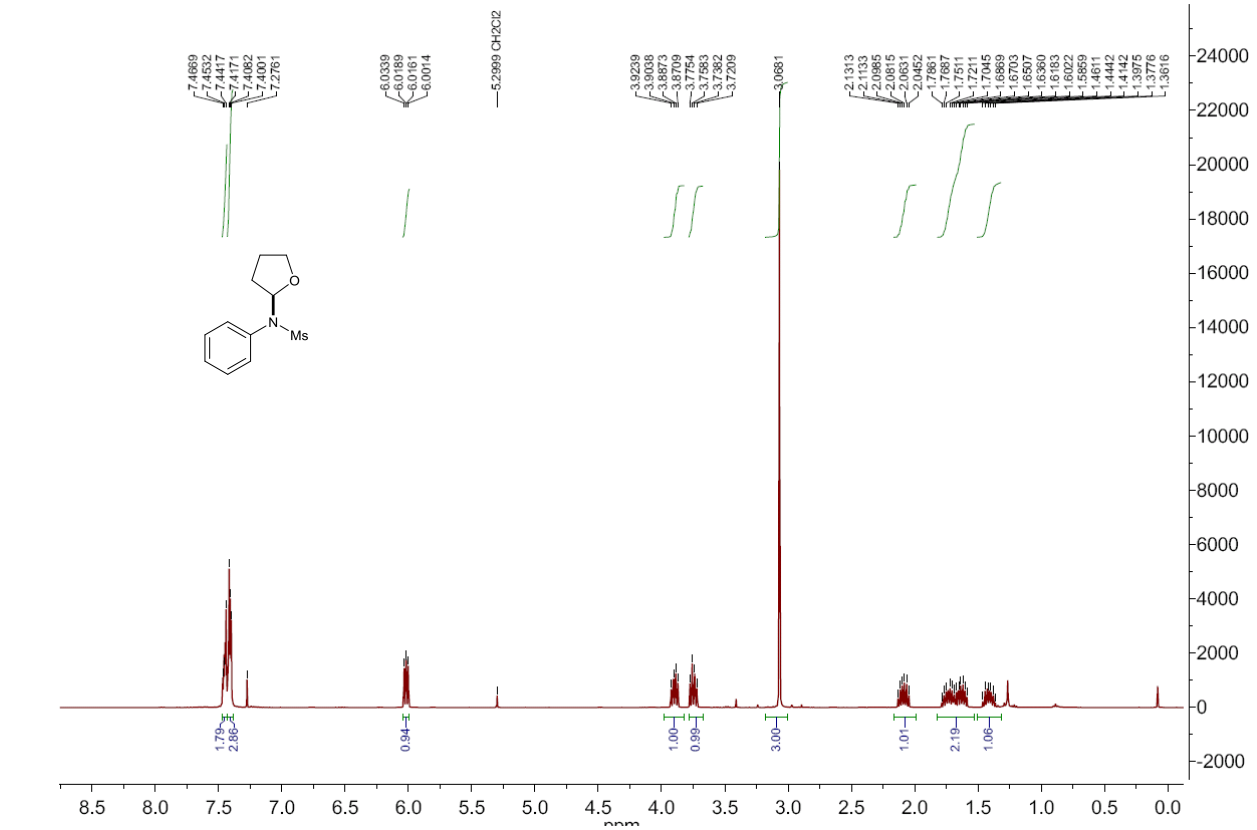


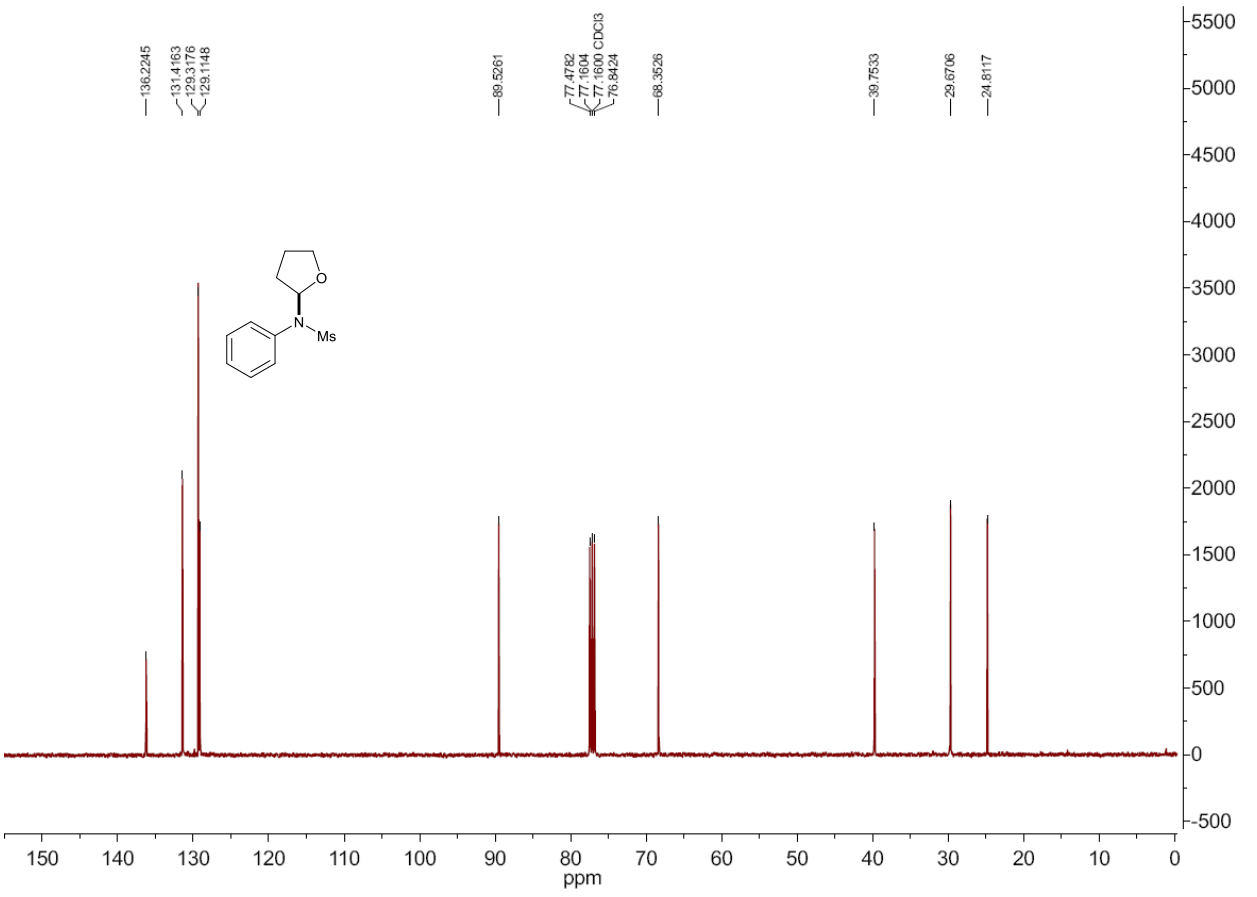
^{1}H and ^{13}C NMR of N-(1-phenylethyl)-N-(tetrahydrofuran-2-yl)methanesulfonamide (d.r. 2:3) minor isomer (3g)



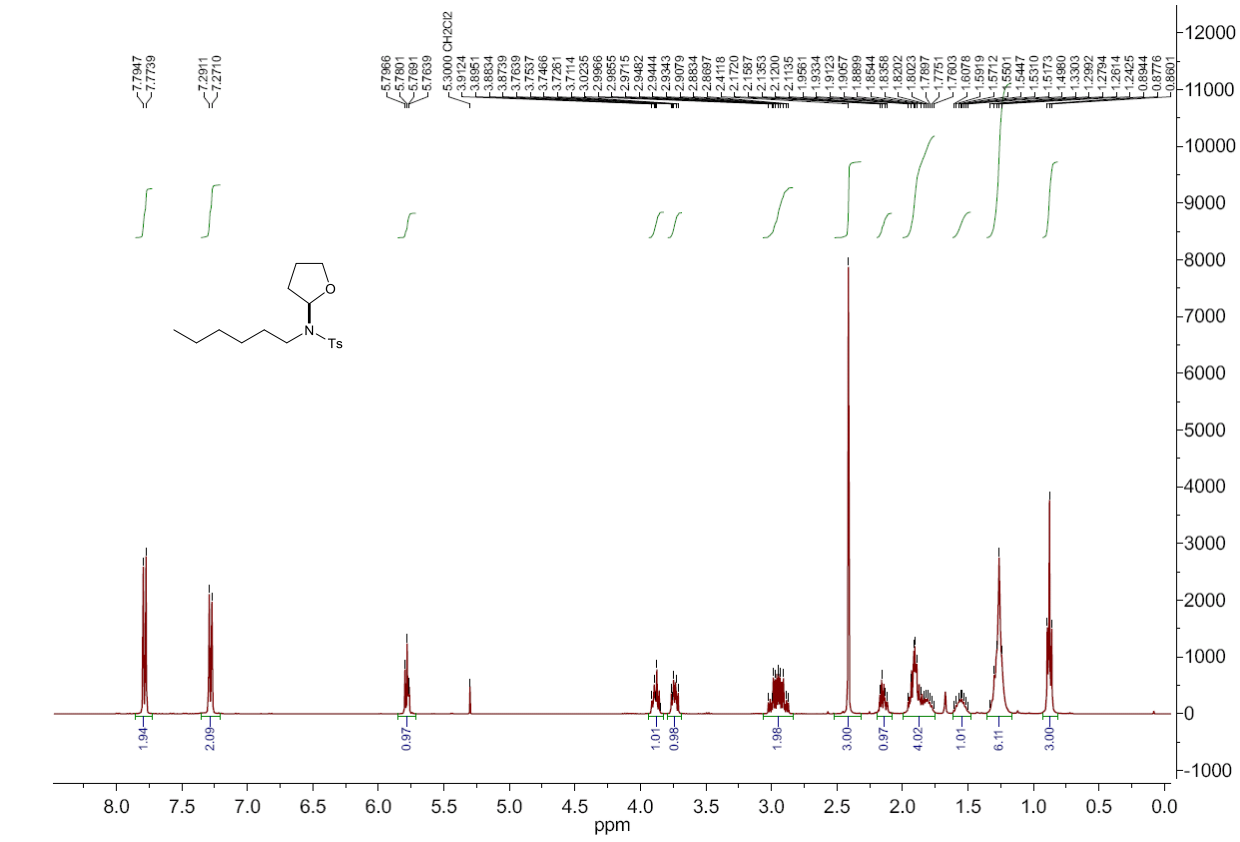


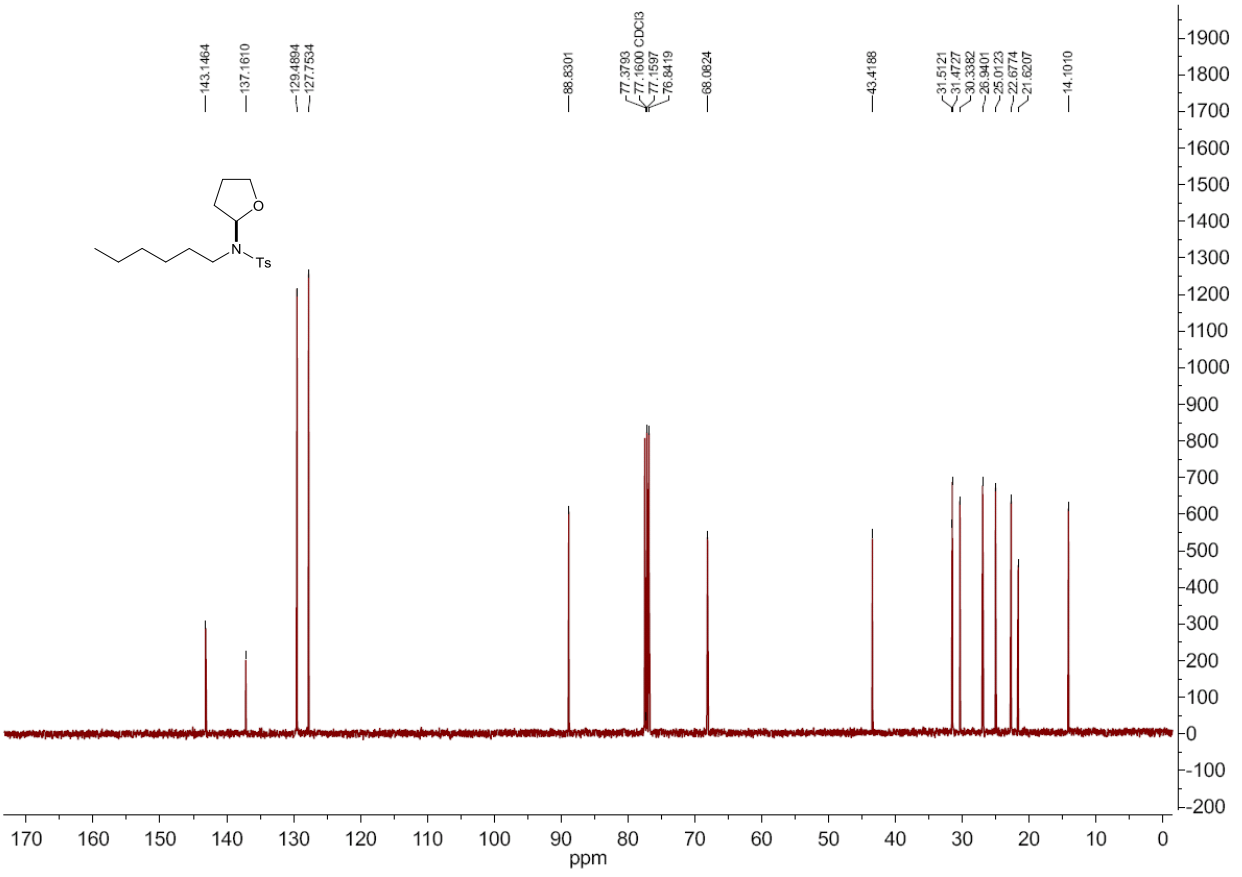
^{1}H and ^{13}C NMR spectra of N-phenyl-N-(tetrahydrofuran-2-yl)methanesulfonamide (3h)



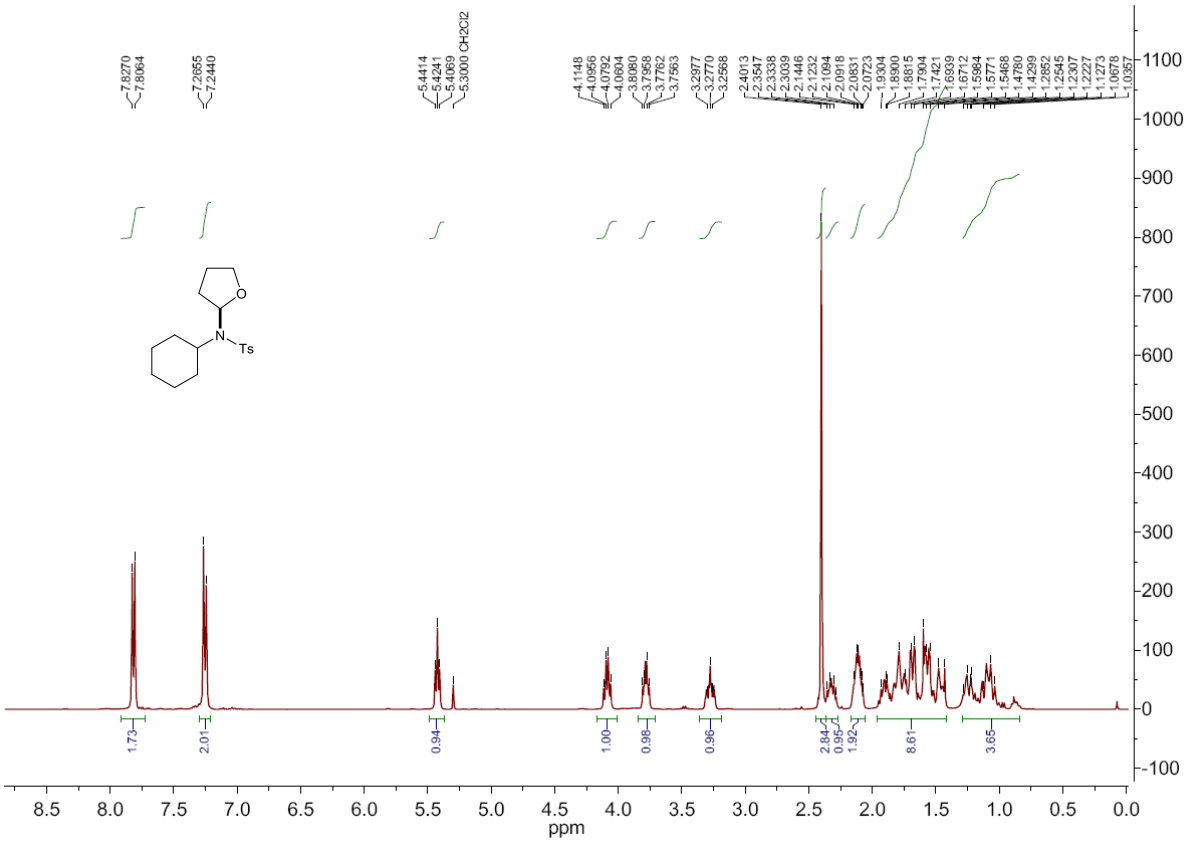


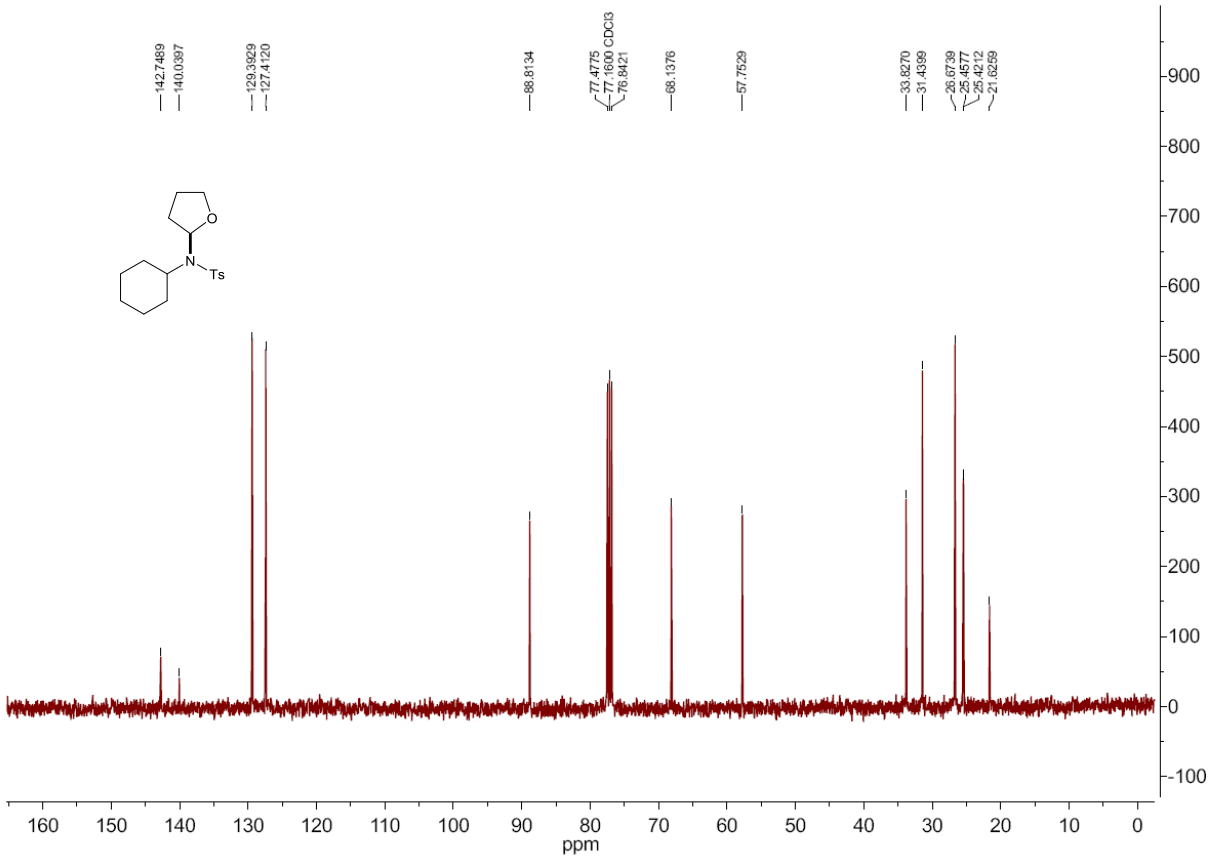
^{1}H and ^{13}C NMR spectra of N-hexyl-4-methyl-N-(tetrahydrofuran-2-yl)benzenesulfonamide (3i)



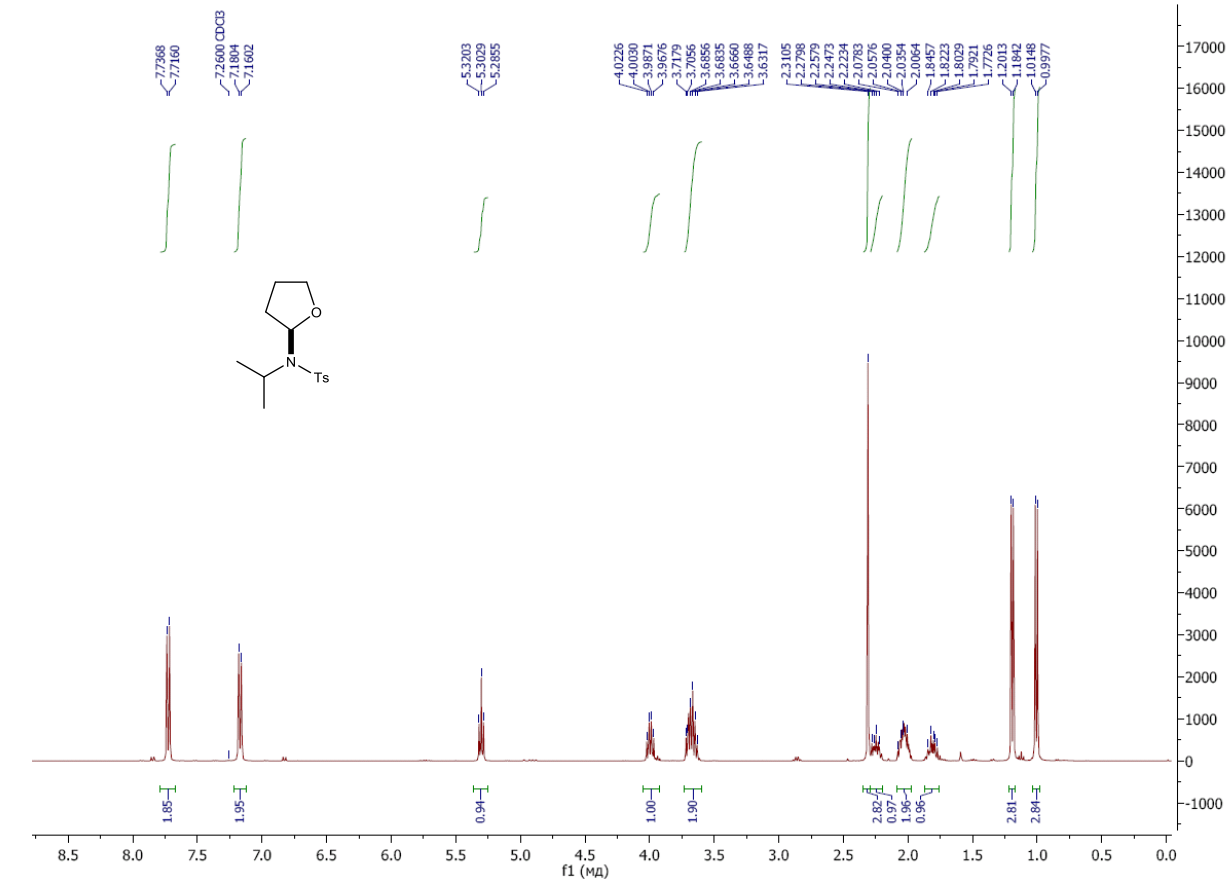


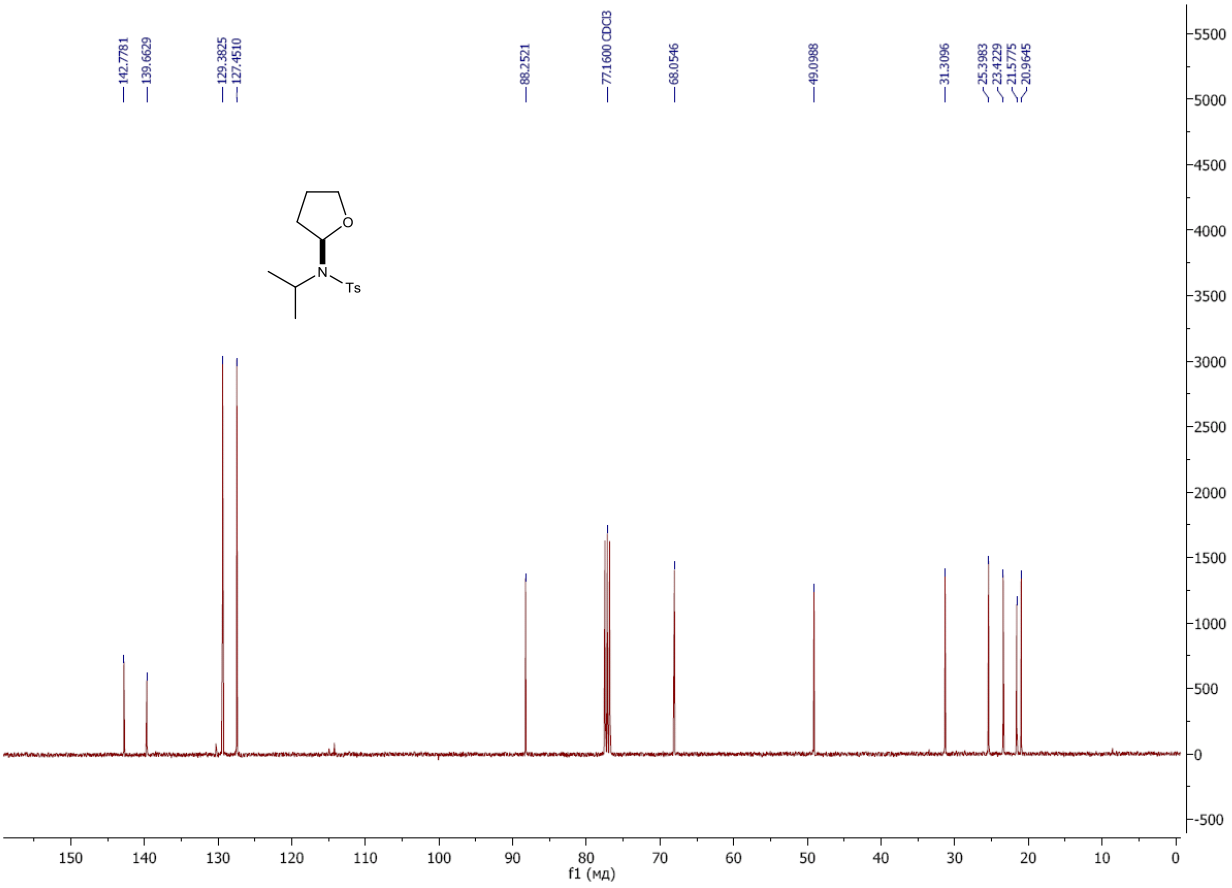
^{1}H and ^{13}C NMR spectra of N-cyclohexyl-4-methyl-N-(tetrahydrofuran-2-yl)benzenesulfonamide (3j)



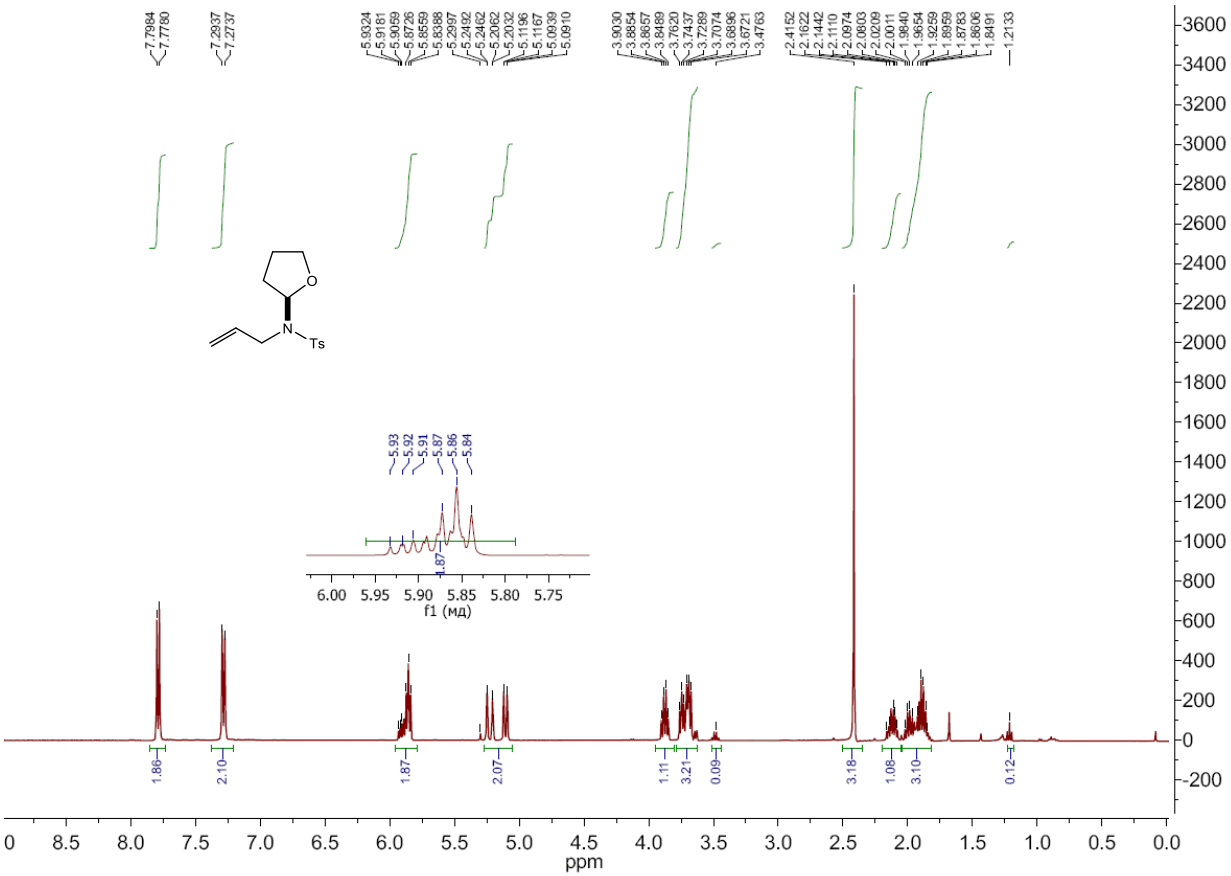


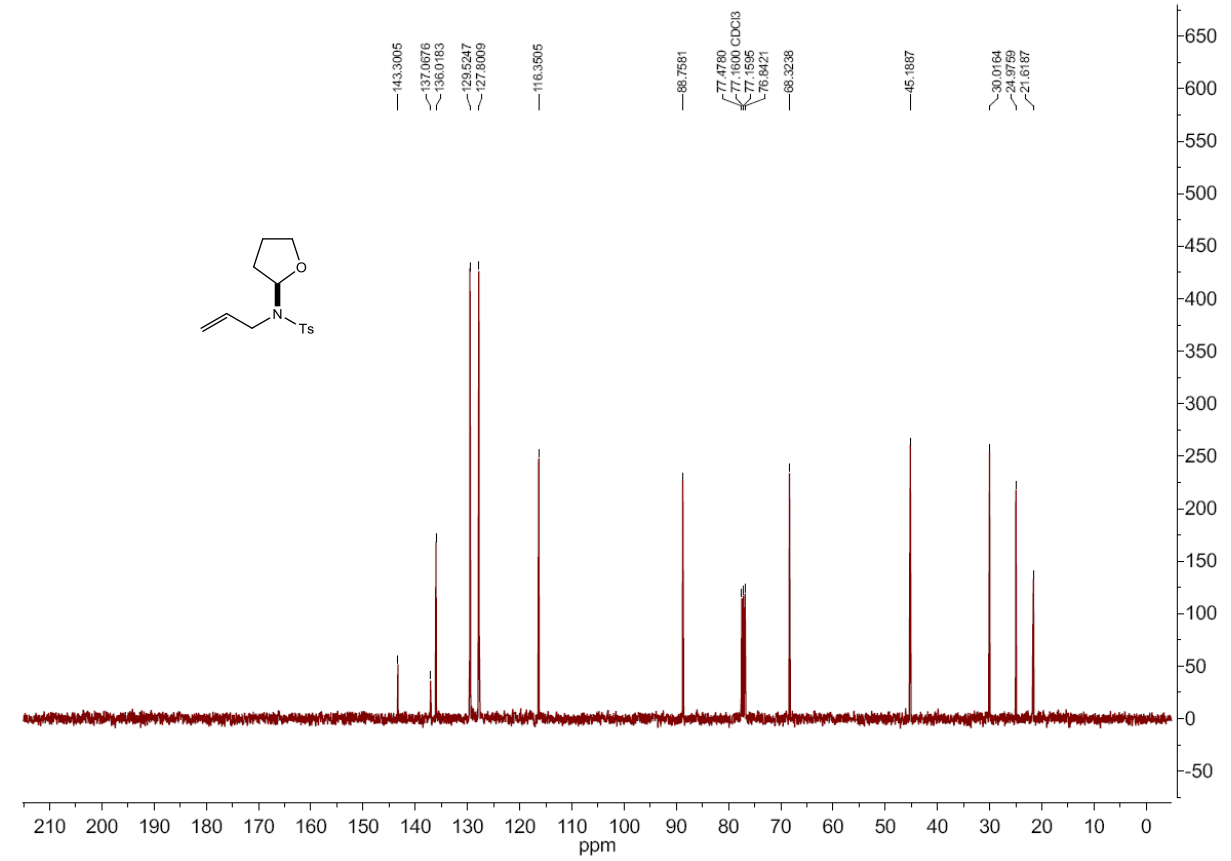
^{1}H and ^{13}C NMR spectra of N-isopropyl-4-methyl-N-(tetrahydrofuran-2-yl)benzenesulfonamide (3k)



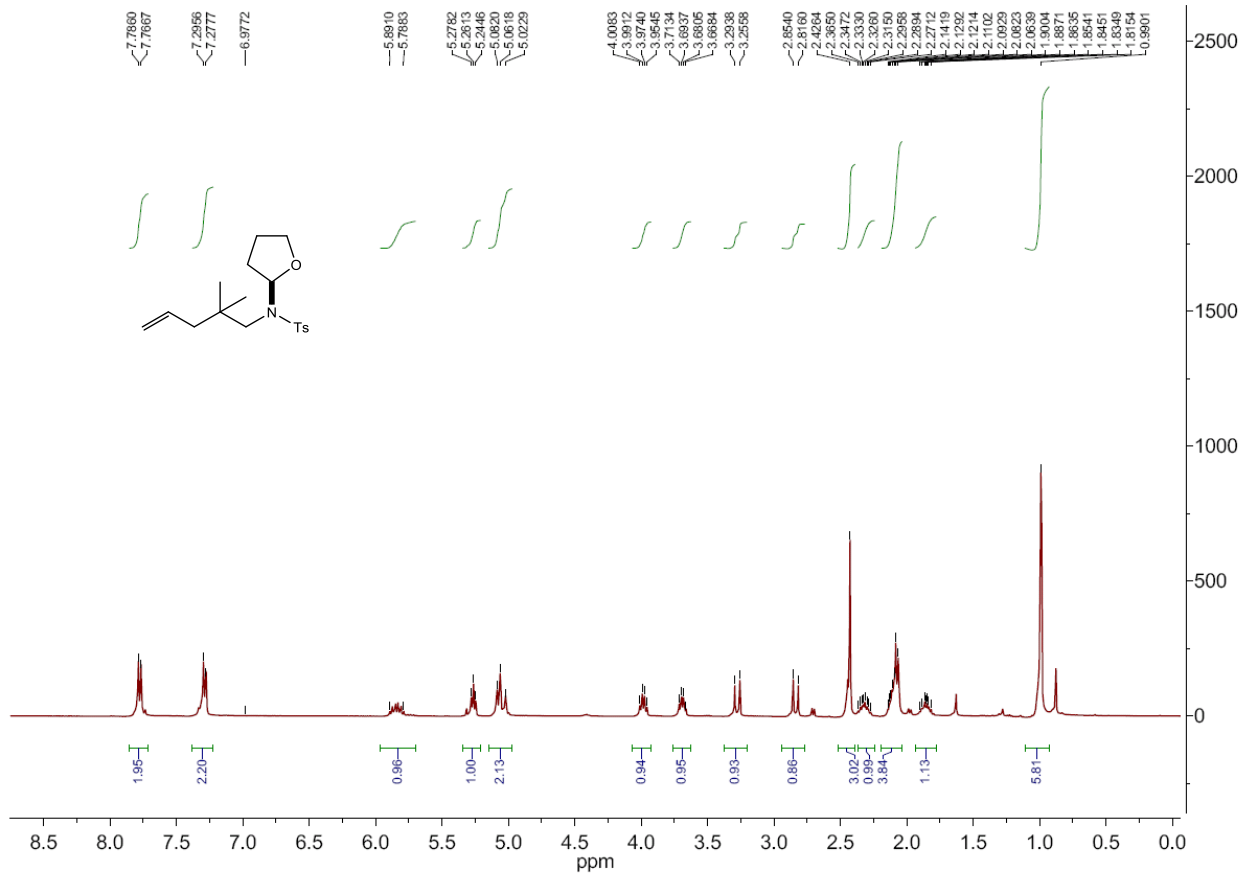


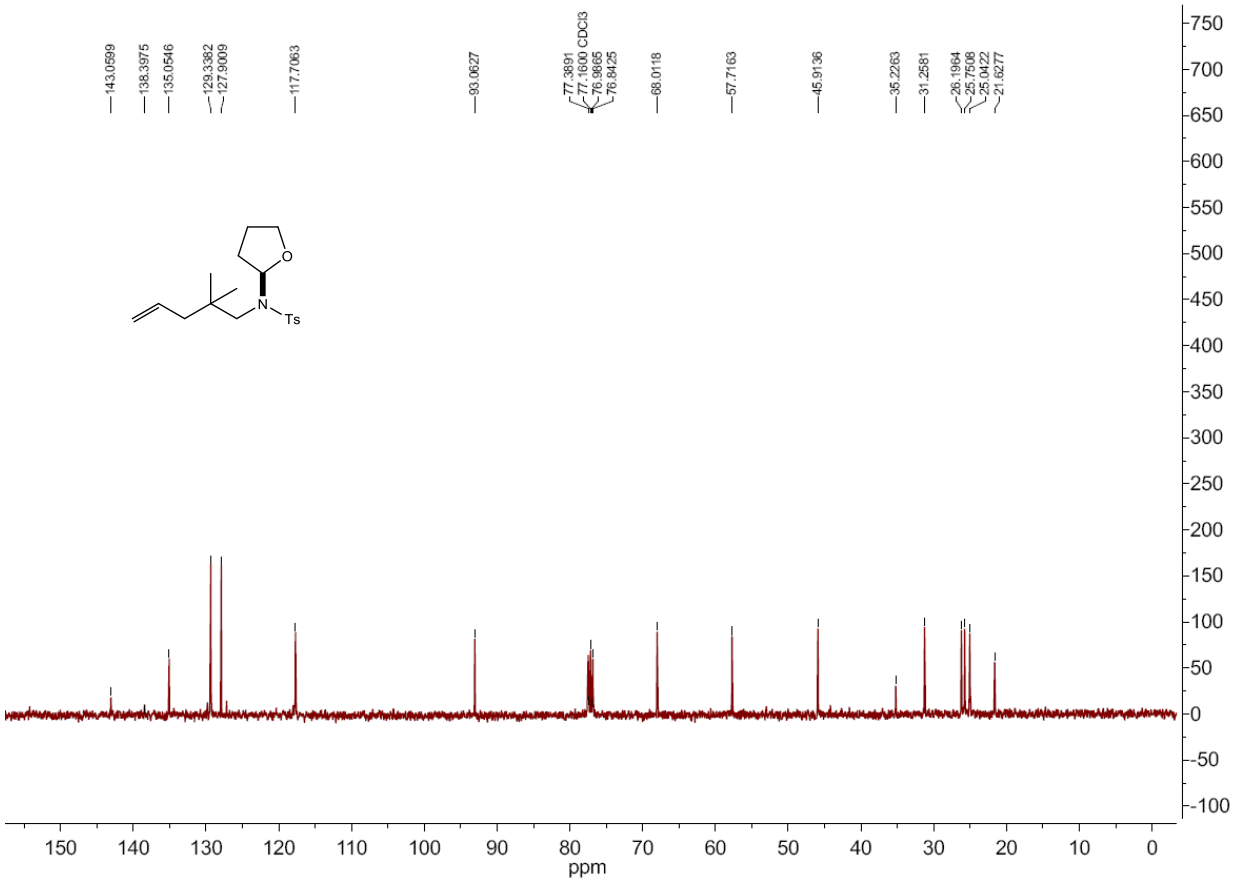
^{1}H and ^{13}C NMR spectra of N-allyl-4-methyl-N-(tetrahydrofuran-2-yl)benzenesulfonamide 8 (3l)



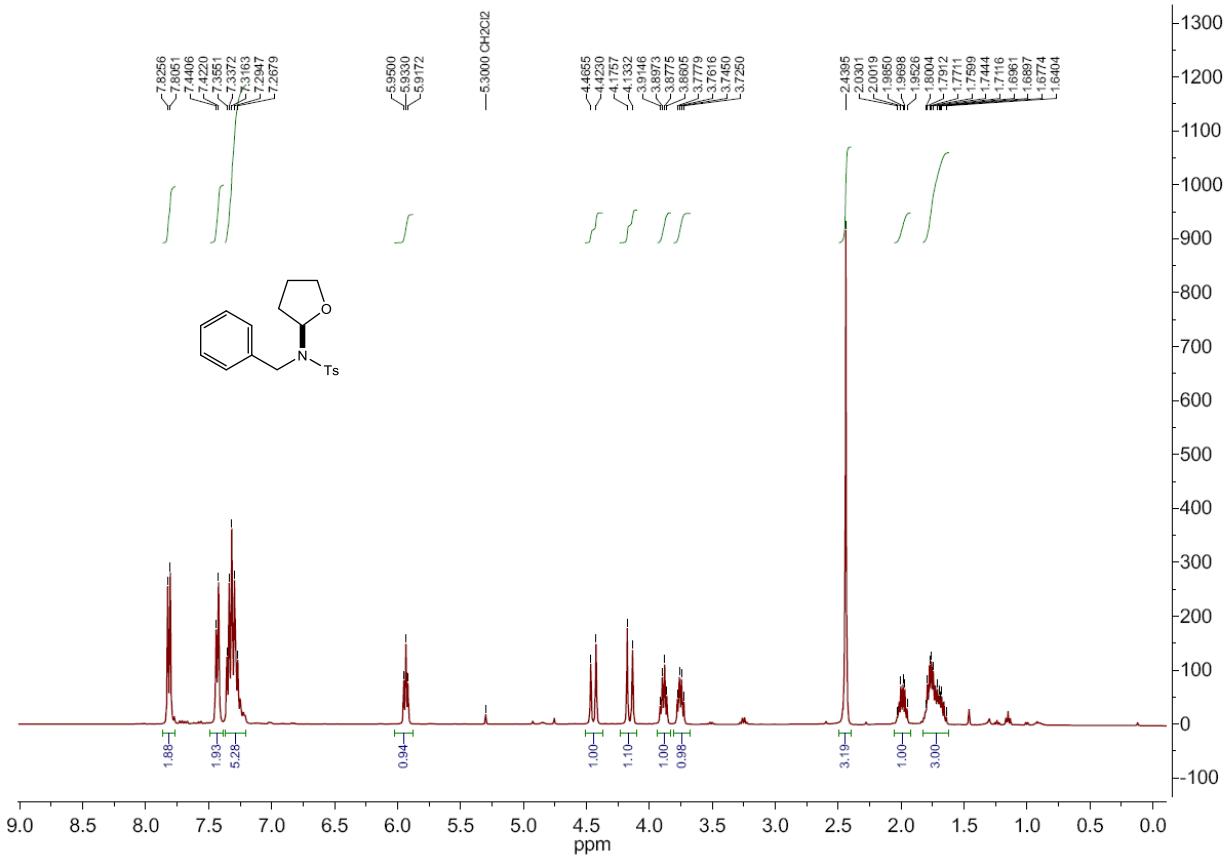


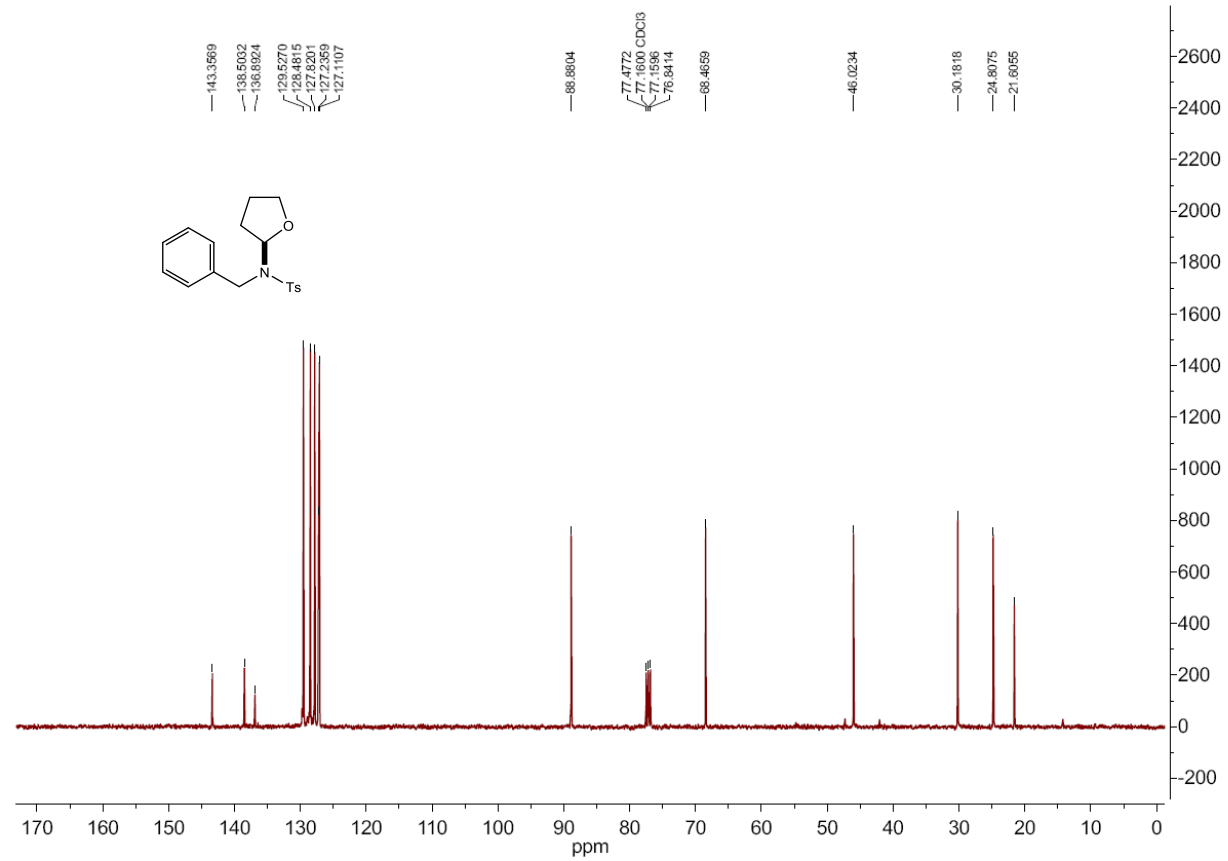
^{1}H and ^{13}C NMR spectra of N-(2,2-dimethylpent-4-en-1-yl)-4-methyl-N-(tetrahydrofuran-2-yl)benzenesulfonamide 2 (3m)



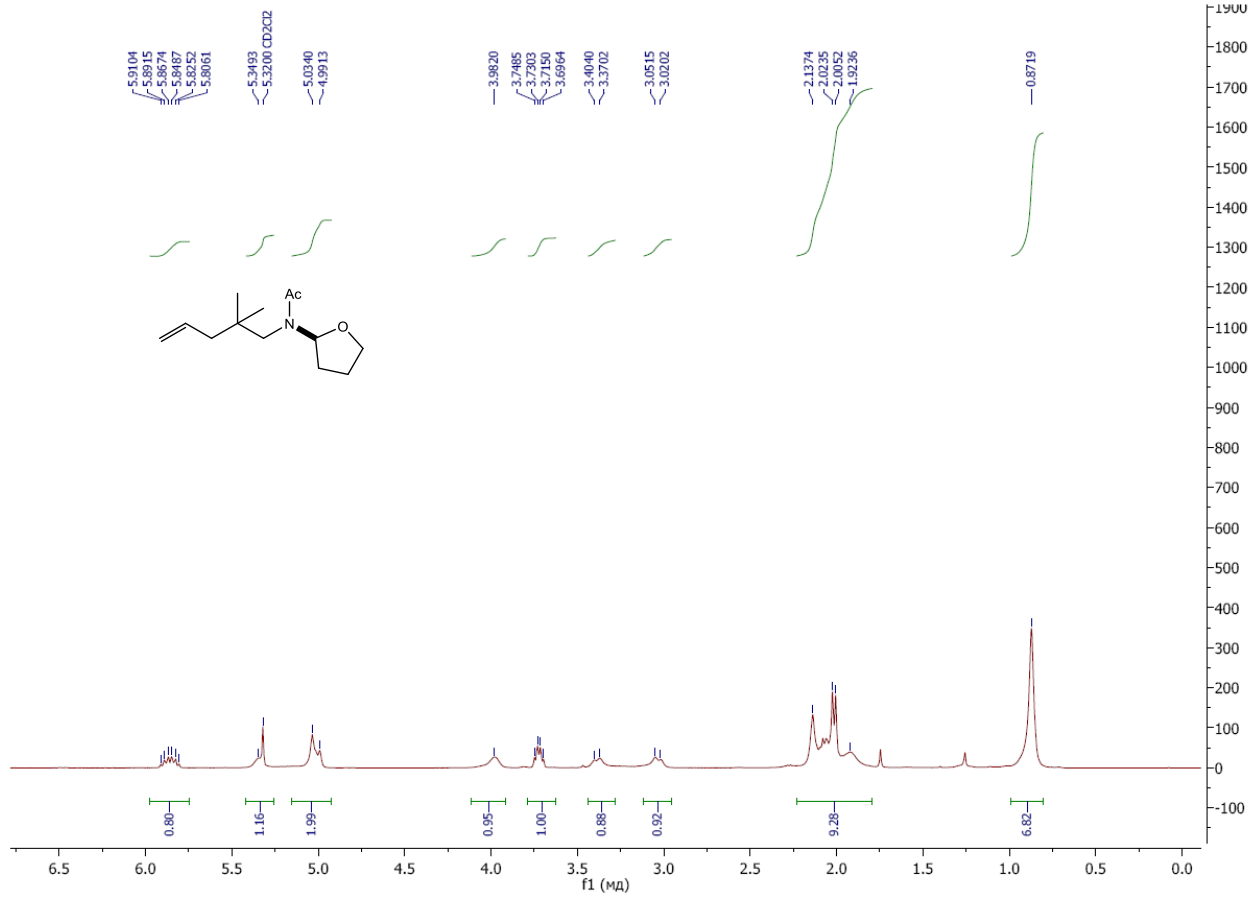


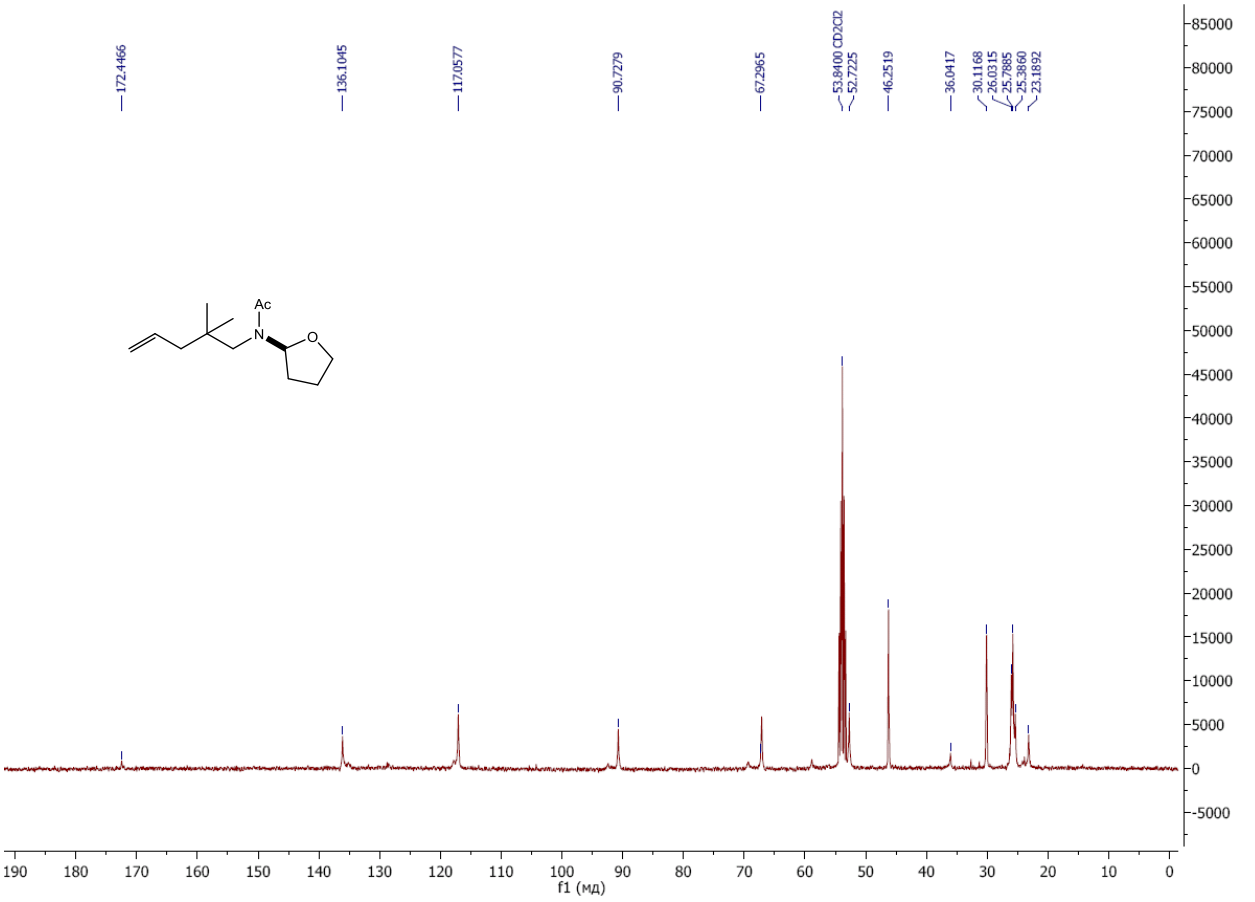
^{1}H and ^{13}C NMR spectra of N-benzyl-4-methyl-N-(tetrahydrofuran-2-yl)benzenesulfonamide (3n)



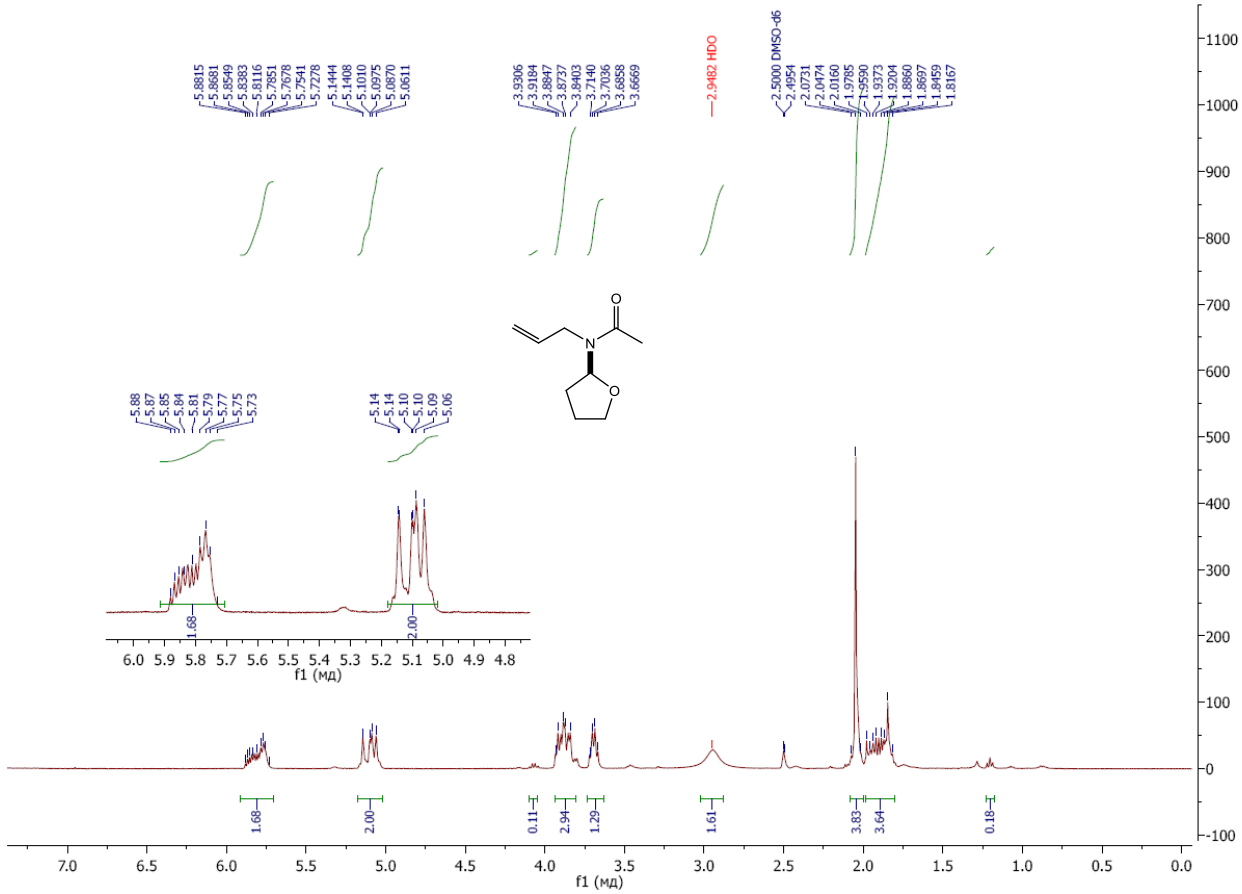


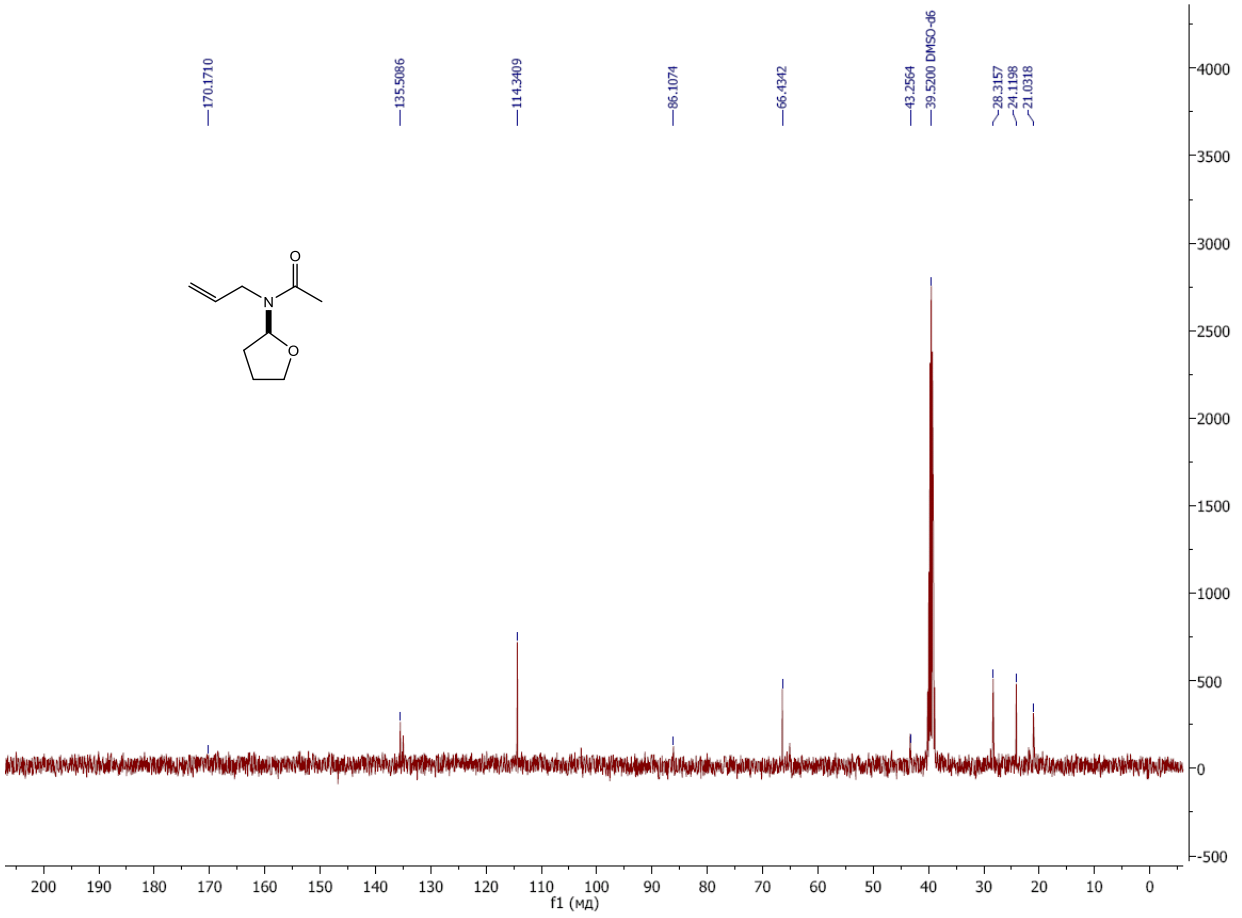
^{1}H and ^{13}C NMR spectra of N-(2,2-dimethylpent-4-en-1-yl)-N-(tetrahydrofuran-2-yl)acetamide (5a)



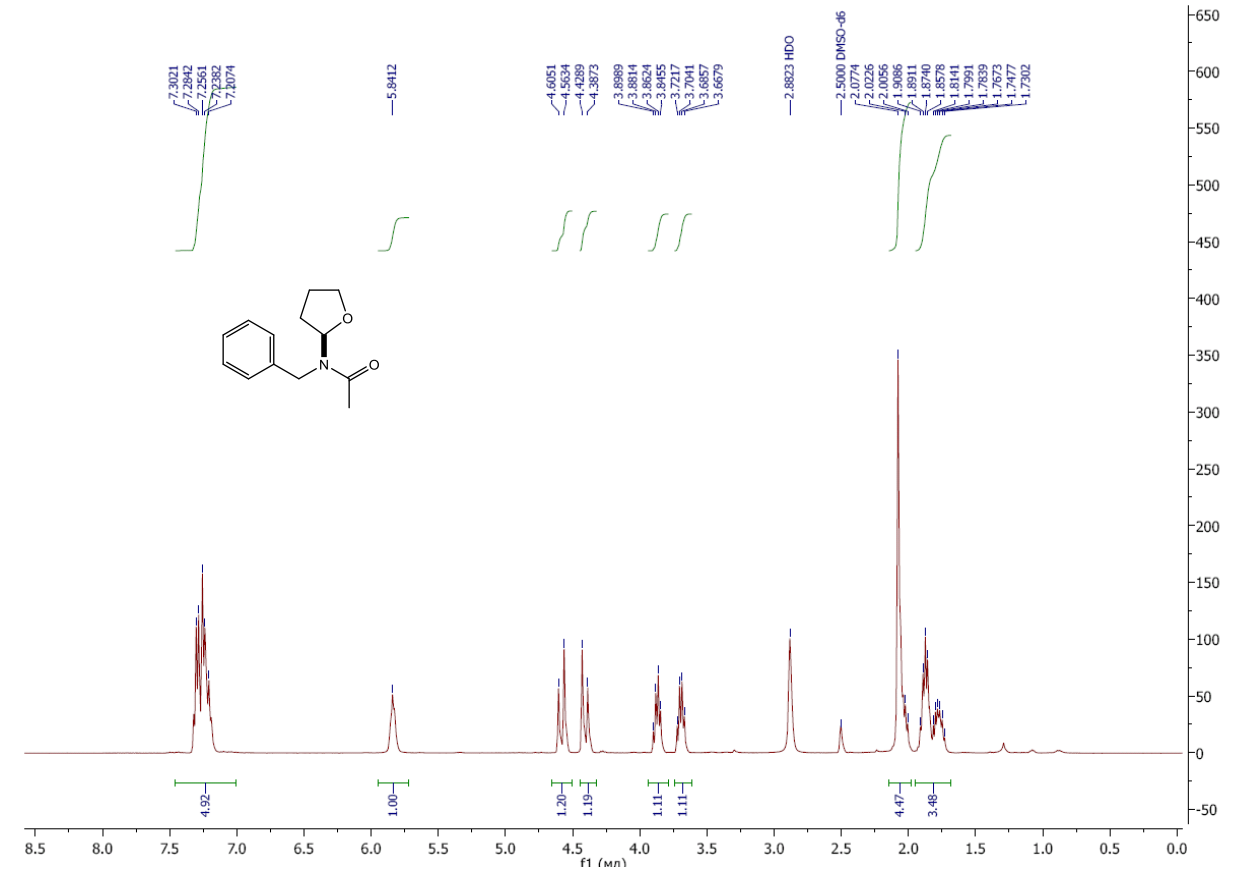


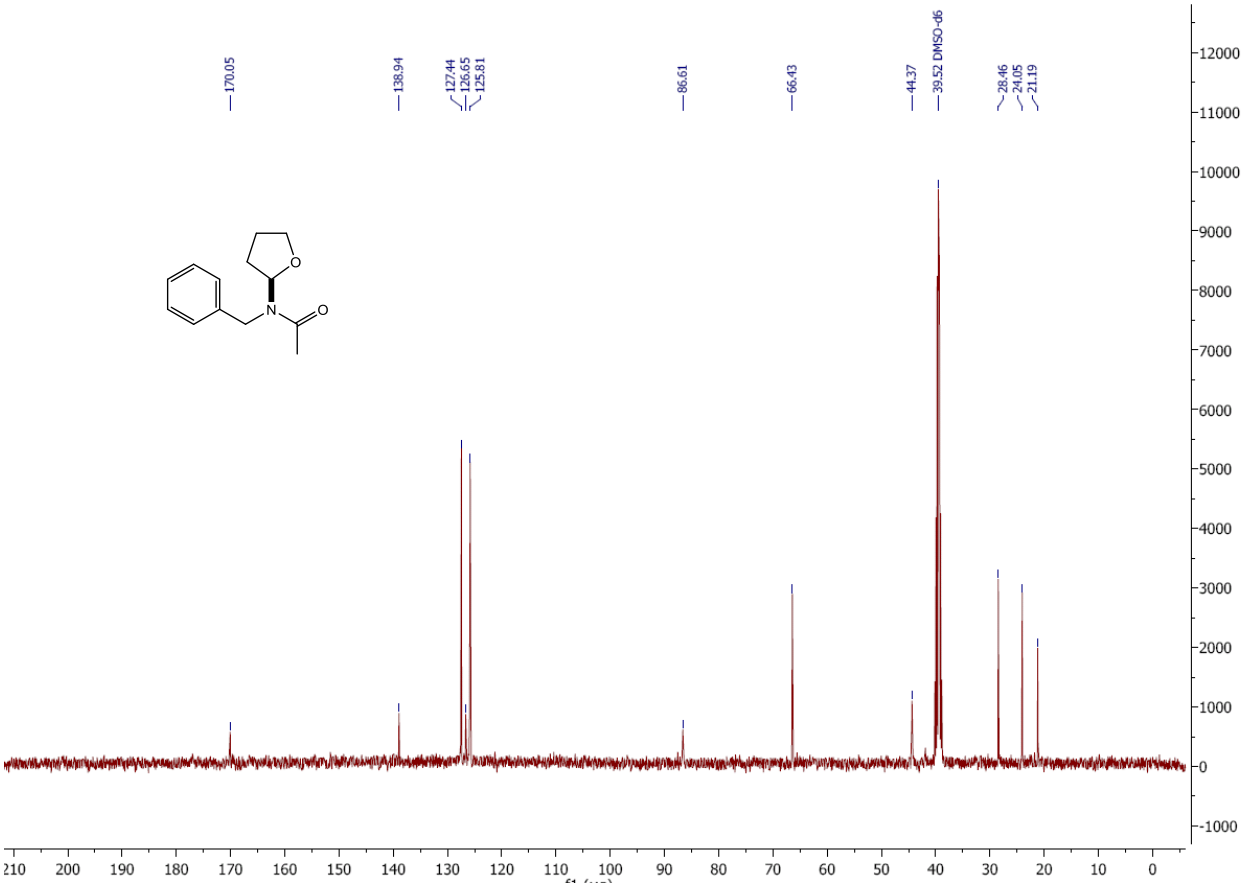
^{1}H and ^{13}C NMR spectra of N-allyl-N-(tetrahydrofuran-2-yl)acetamide (5b)



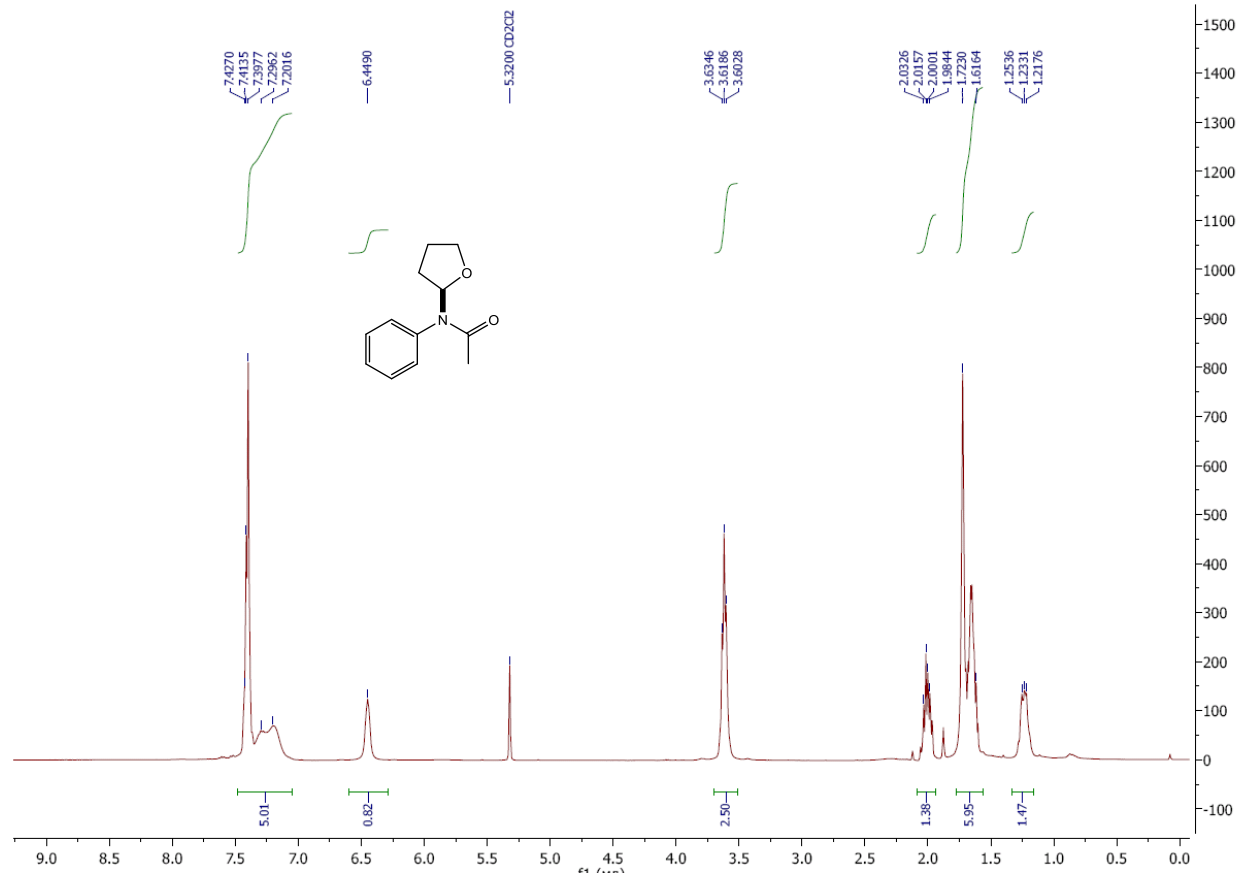


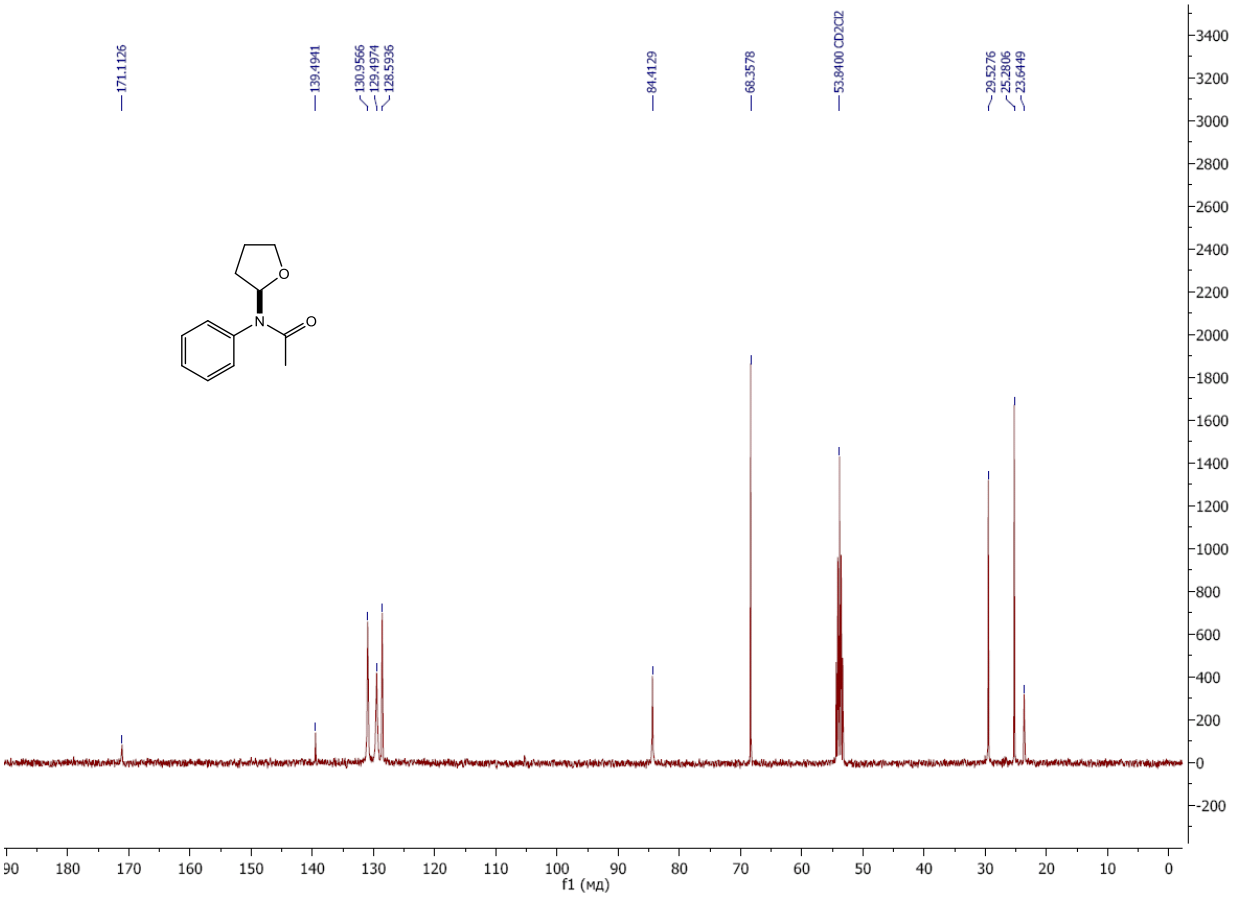
^{1}H and ^{13}C NMR spectra of N-benzyl-N-(tetrahydrofuran-2-yl)acetamide (5c)



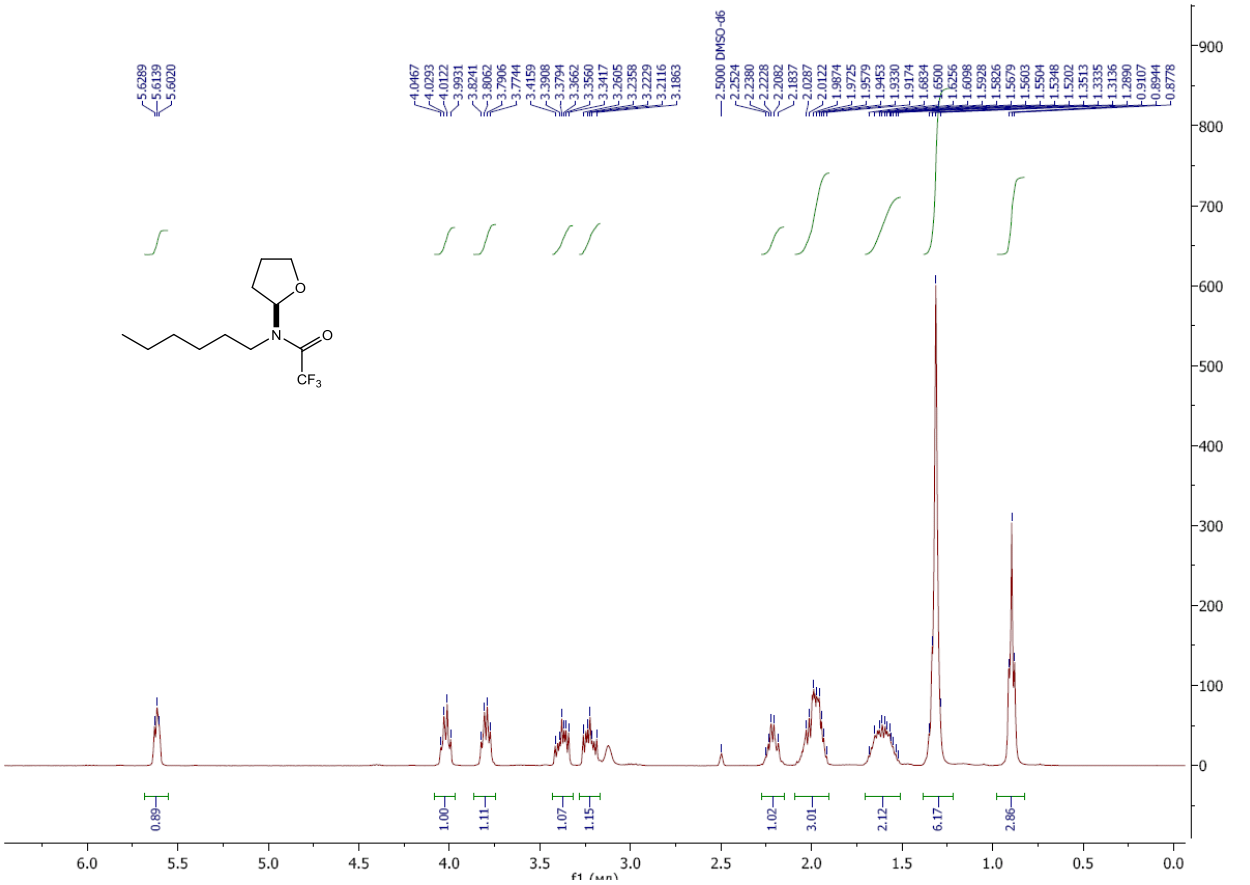


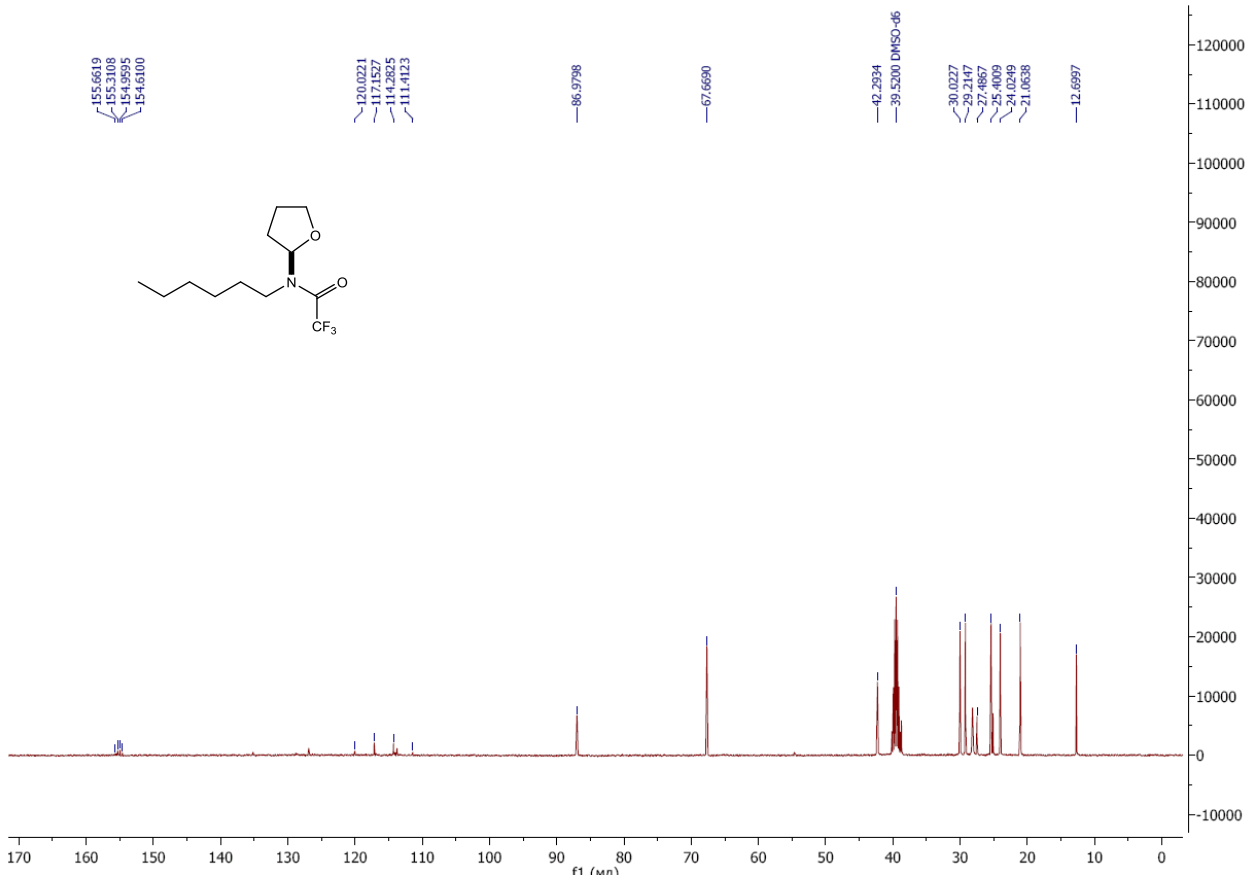
^{1}H and ^{13}C NMR spectra of N-phenyl-N-(tetrahydrofuran-2-yl)acetamide (5d)



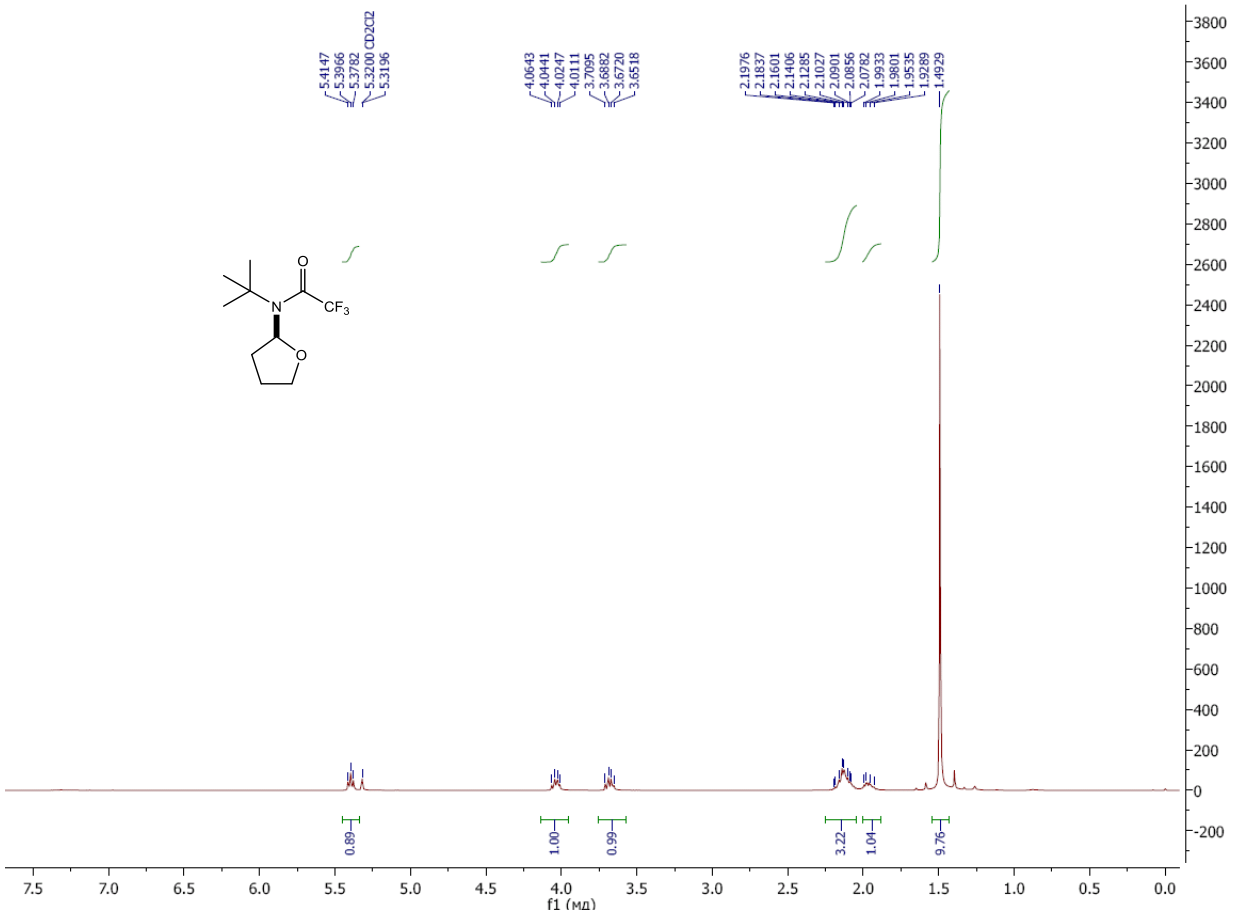


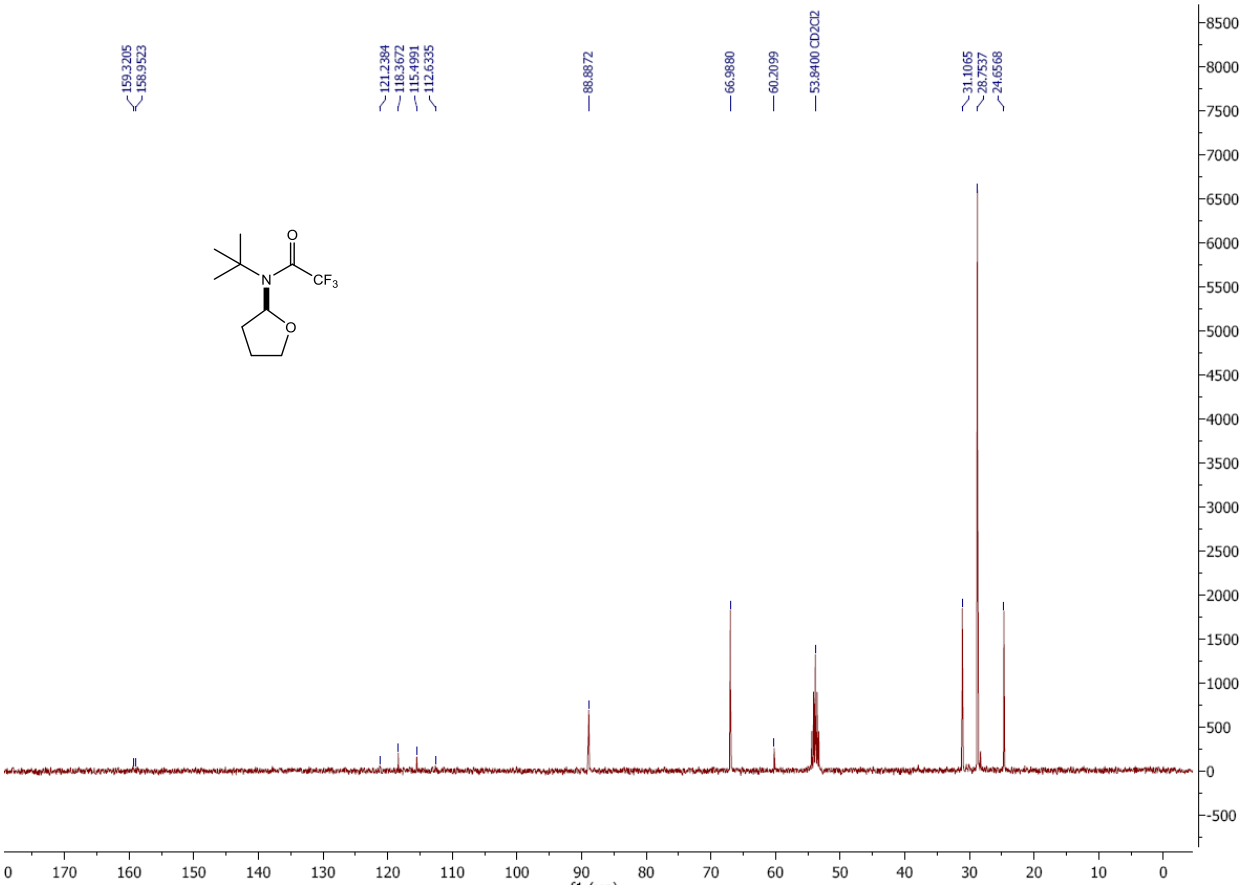
^{1}H and ^{13}C NMR spectra of 2,2,2-trifluoro-N-hexyl-N-(tetrahydrofuran-2-yl)acetamide (5e)



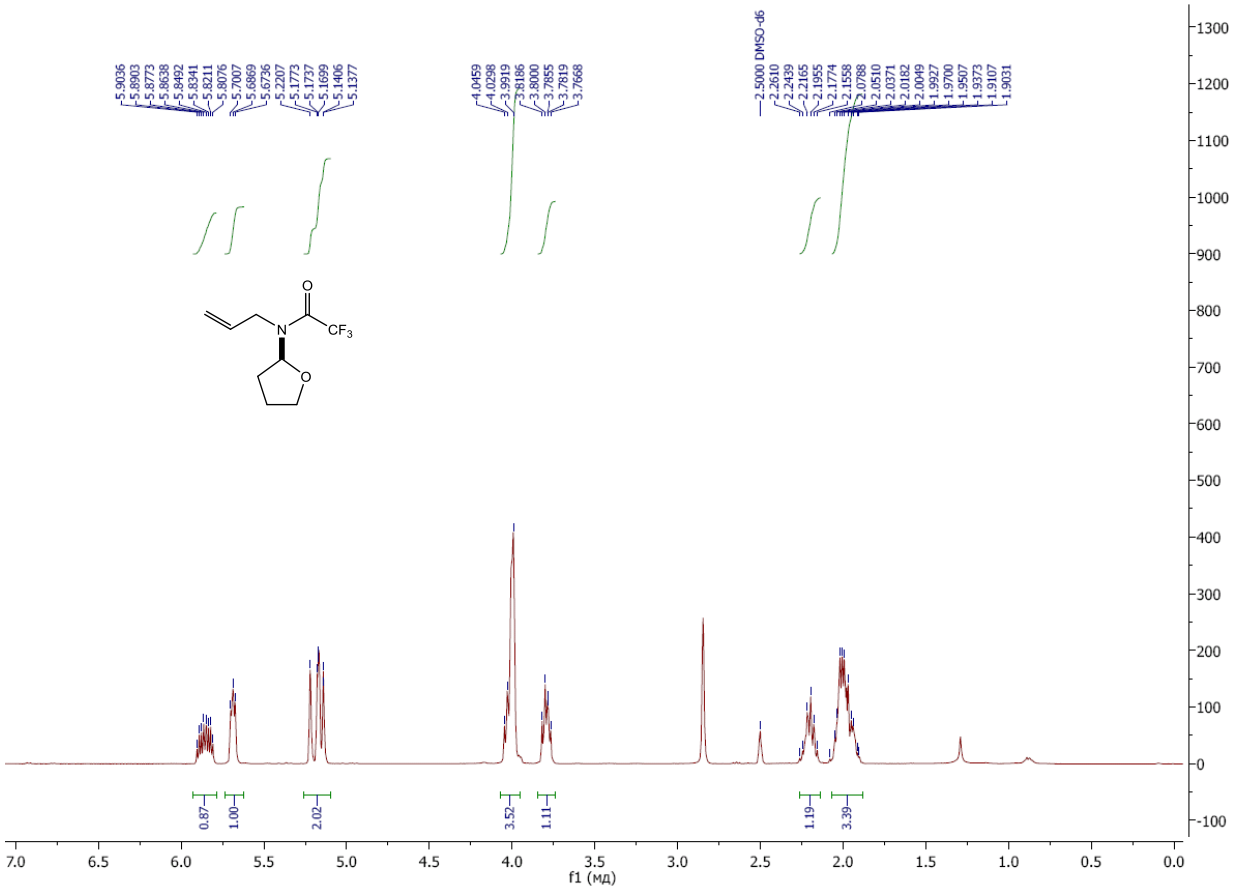


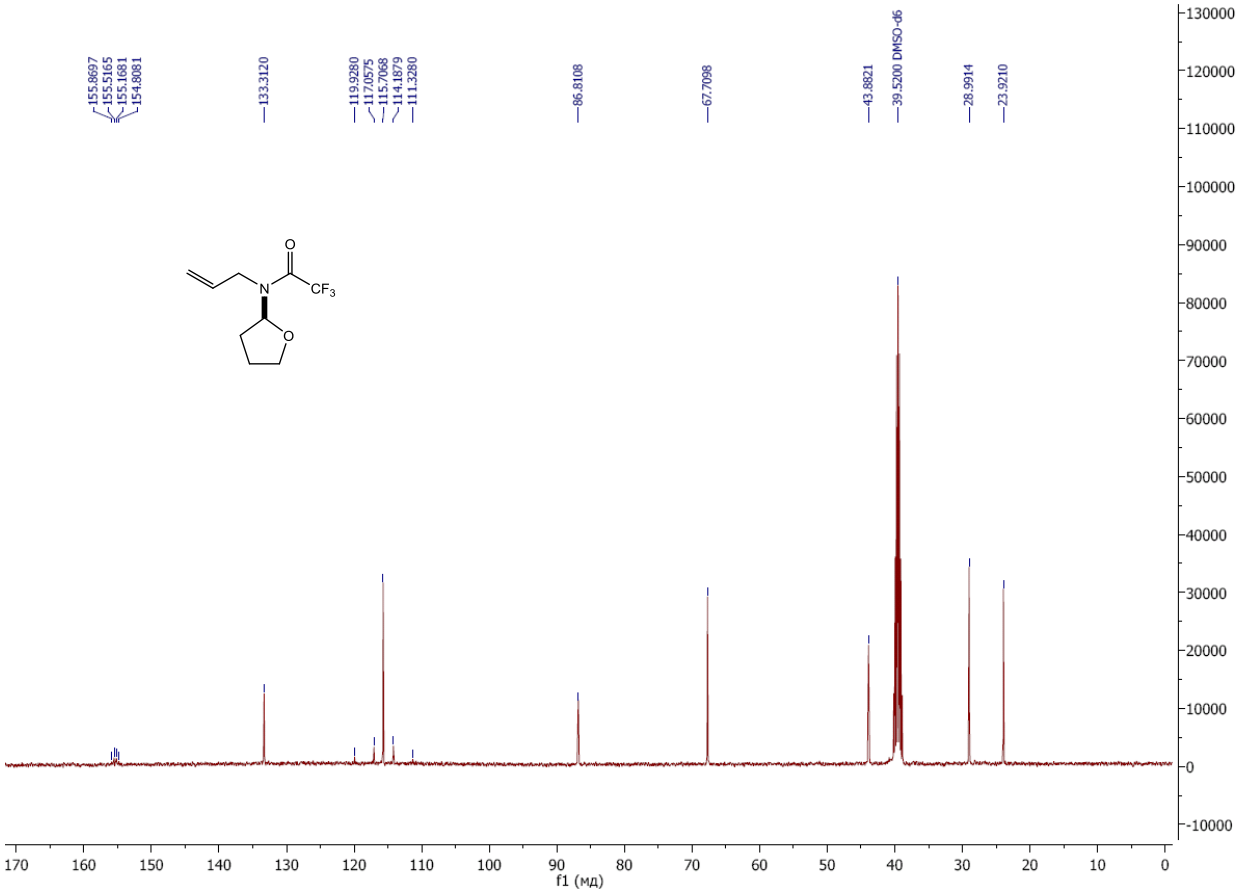
^{1}H and ^{13}C NMR spectra of N-(tert-butyl)-2,2,2-trifluoro-N-(tetrahydrofuran-2-yl)acetamide (5f)



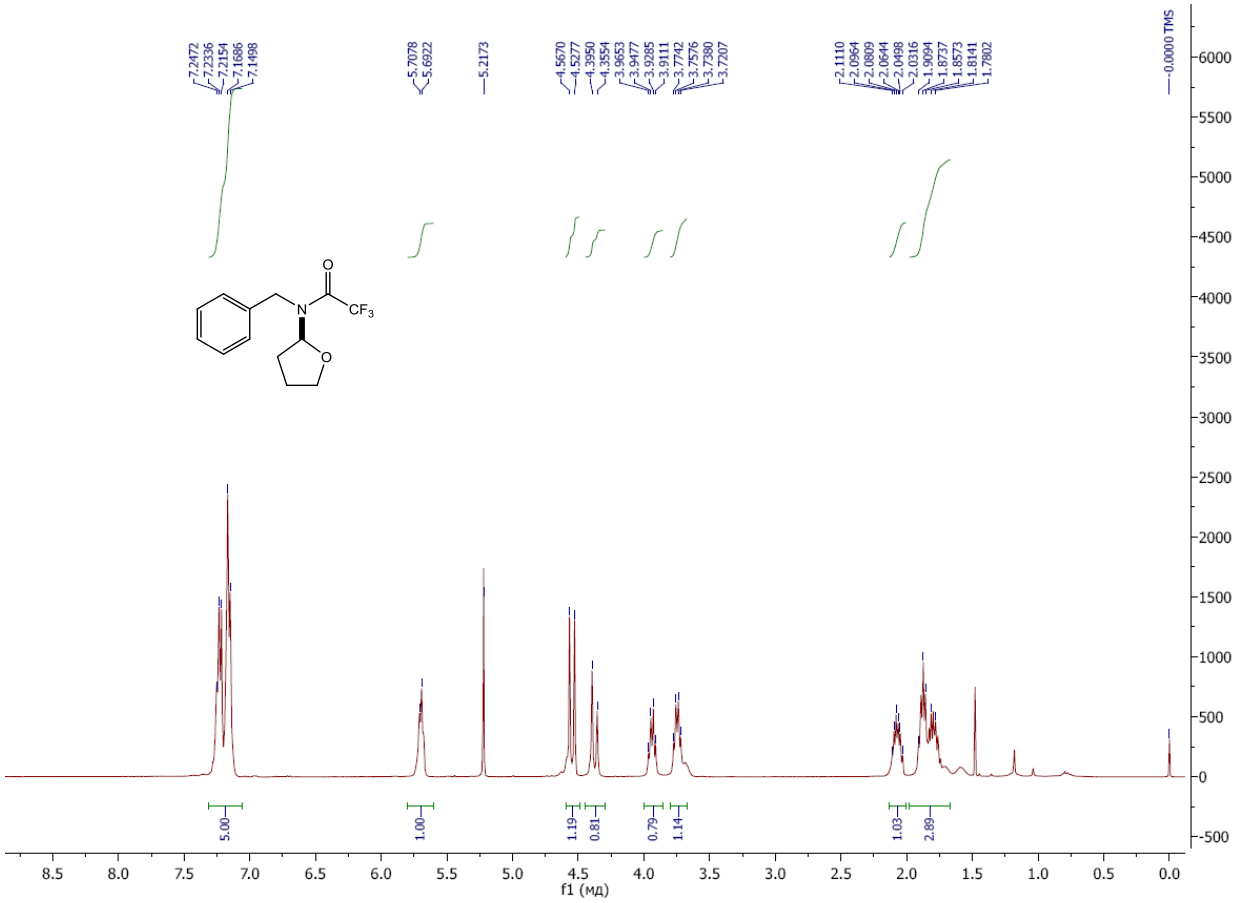


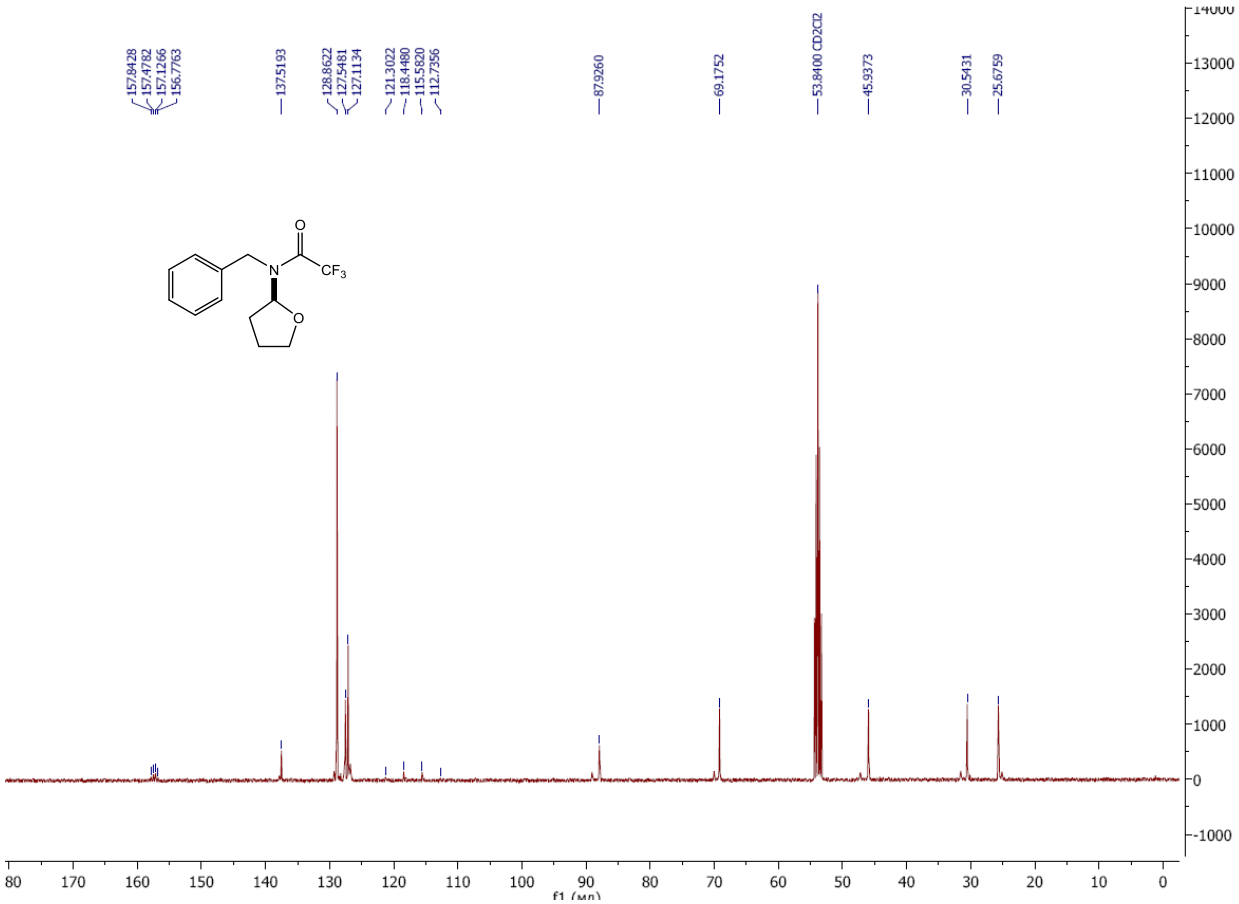
^{1}H and ^{13}C NMR spectra of N-allyl-2,2,2-trifluoro-N-(tetrahydrofuran-2-yl)acetamide (5g)



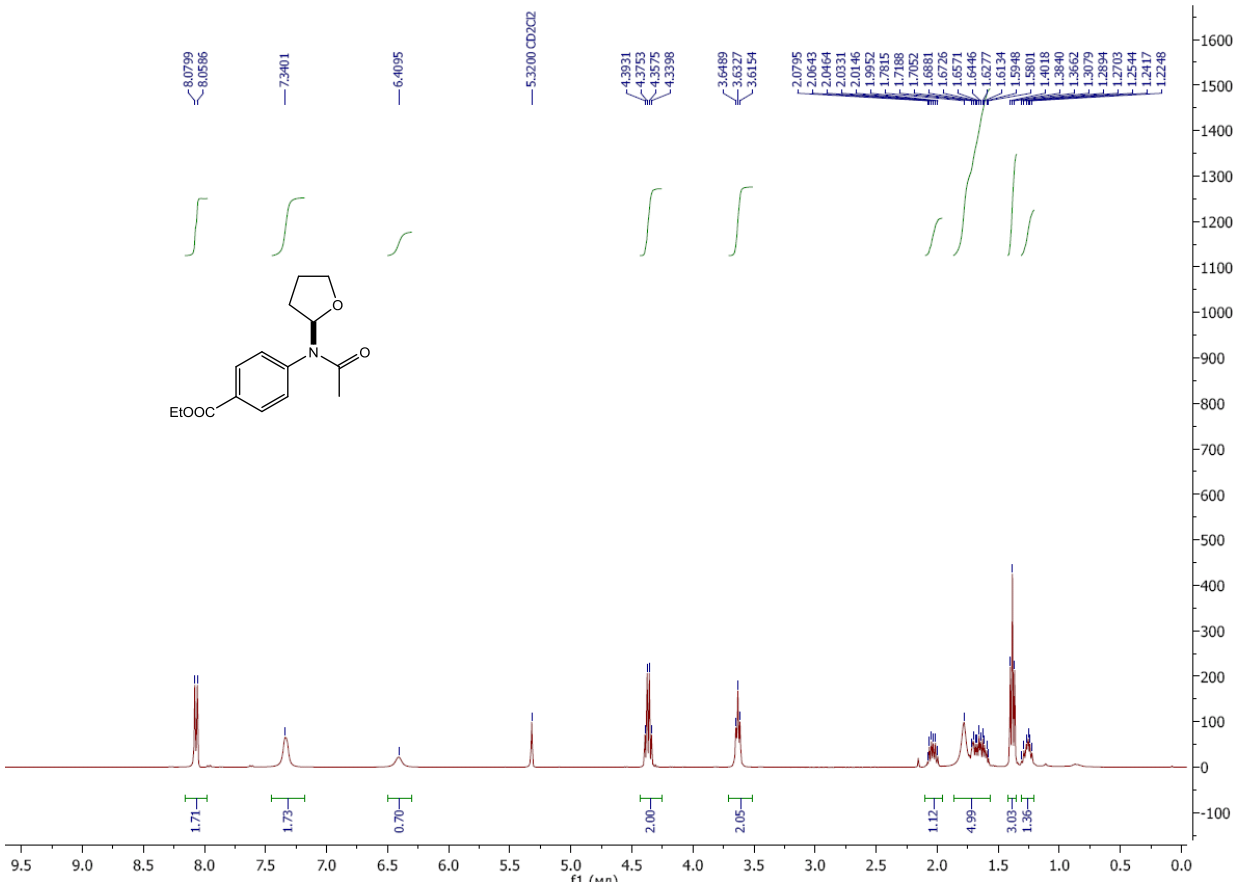


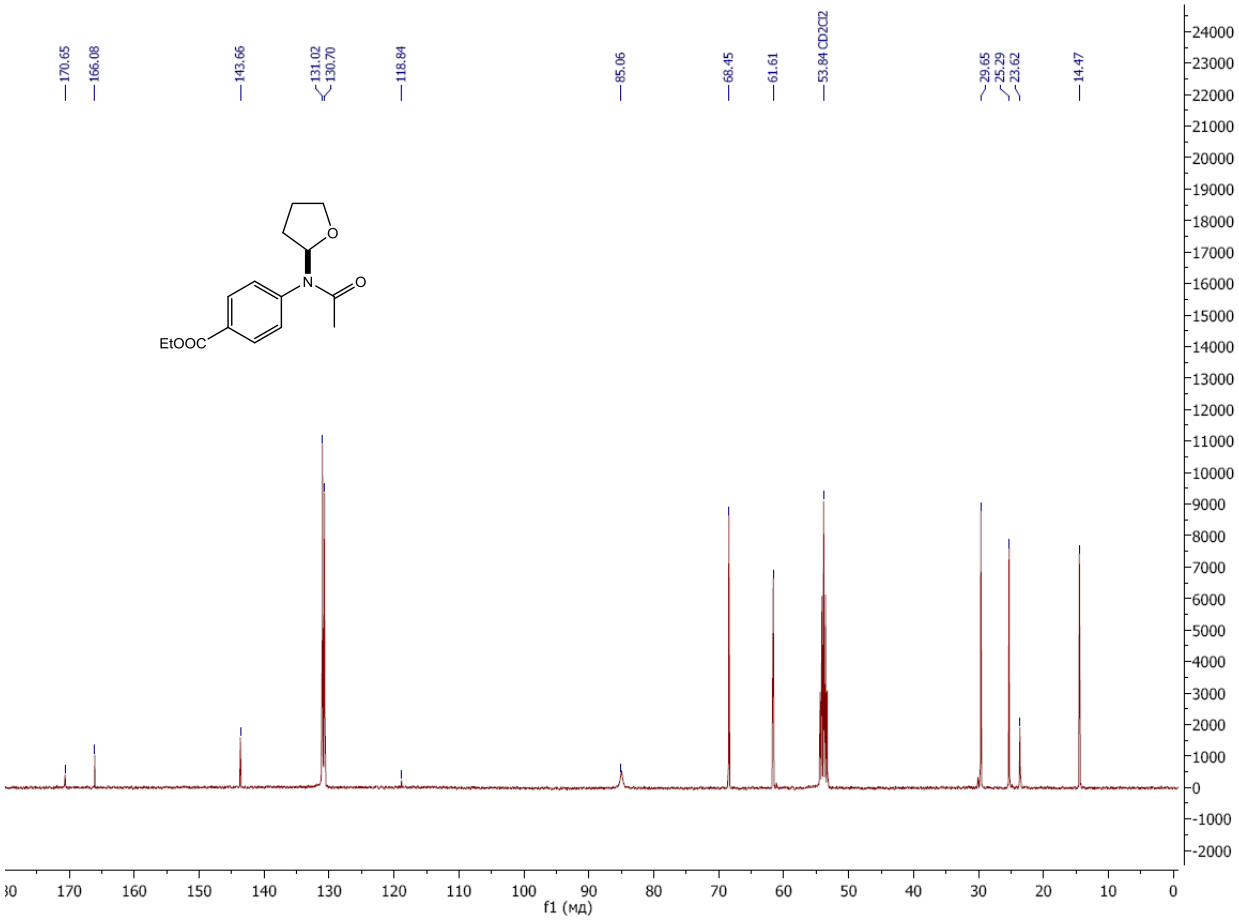
^{1}H and ^{13}C NMR spectra of N-benzyl-2,2,2-trifluoro-N-(tetrahydrofuran-2-yl)acetamide (5h)



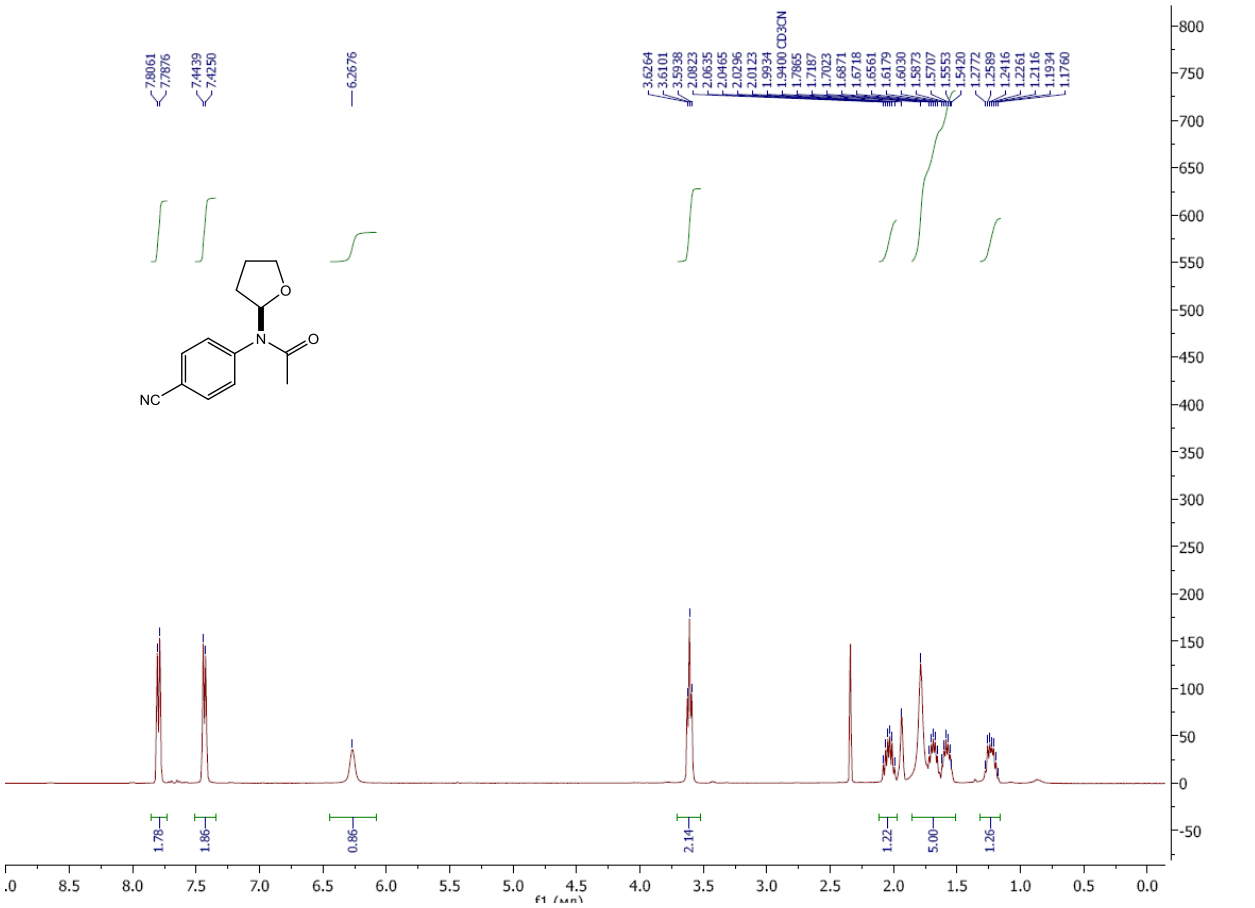


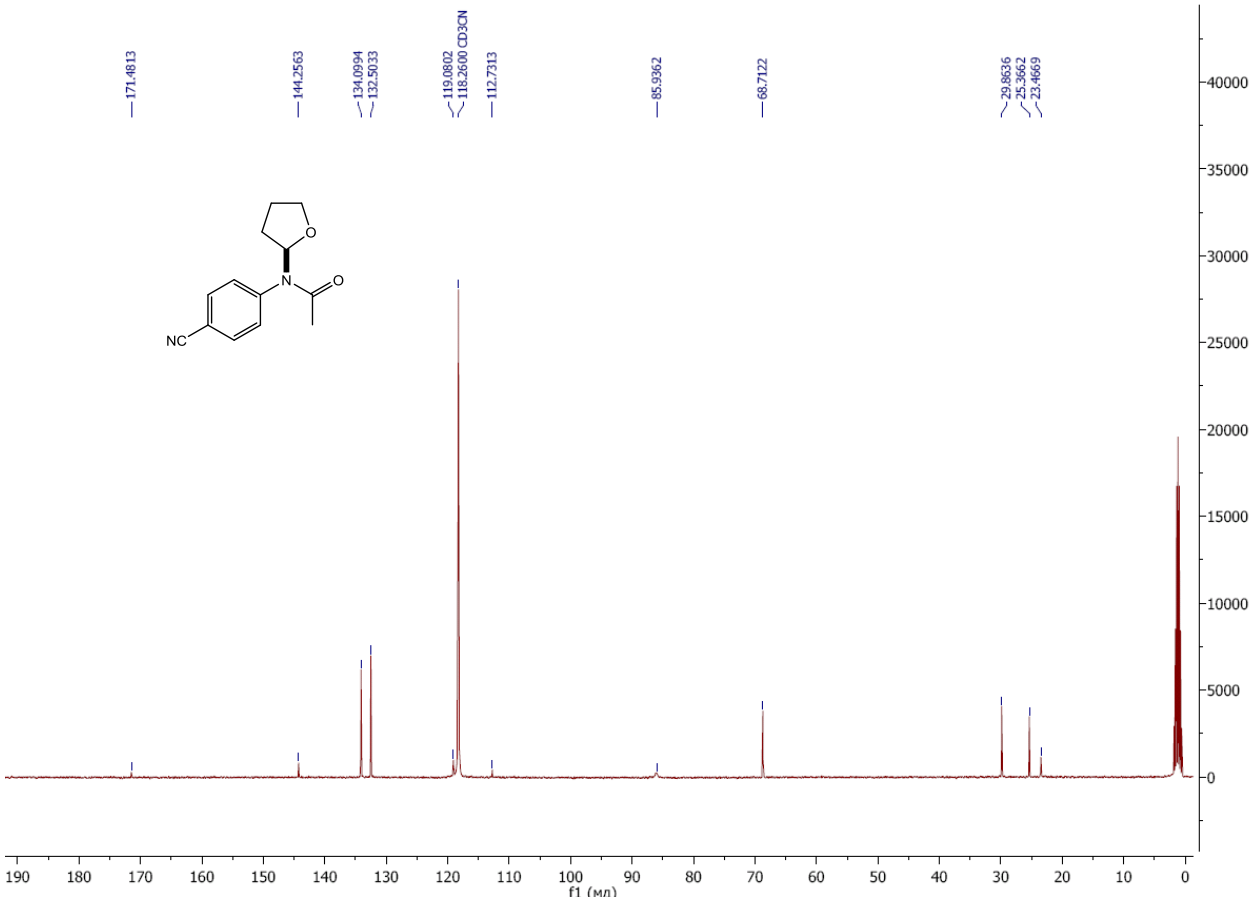
^{1}H and ^{13}C NMR spectra of ethyl-4-(N-(tetrahydrofuran-2-yl)acetamido)benzoate (5i)



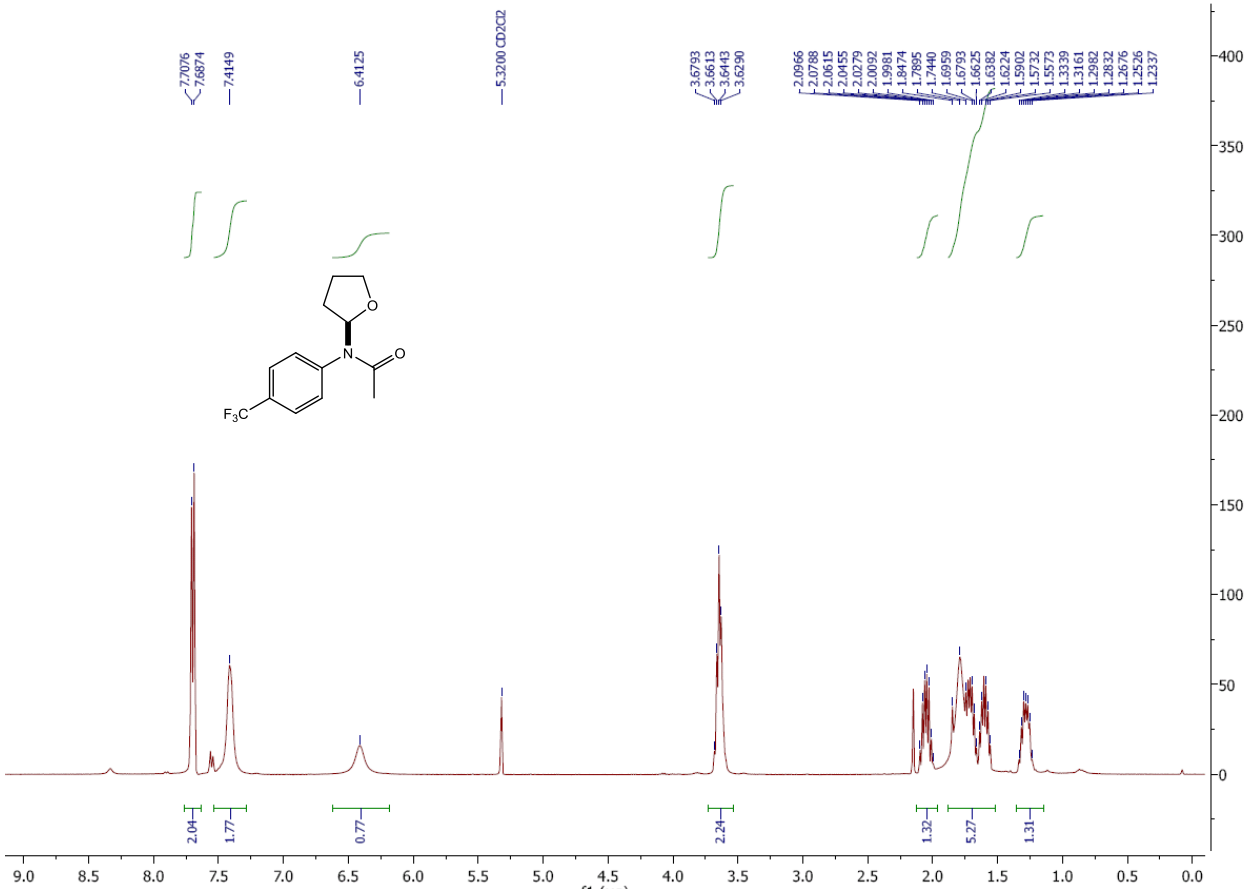


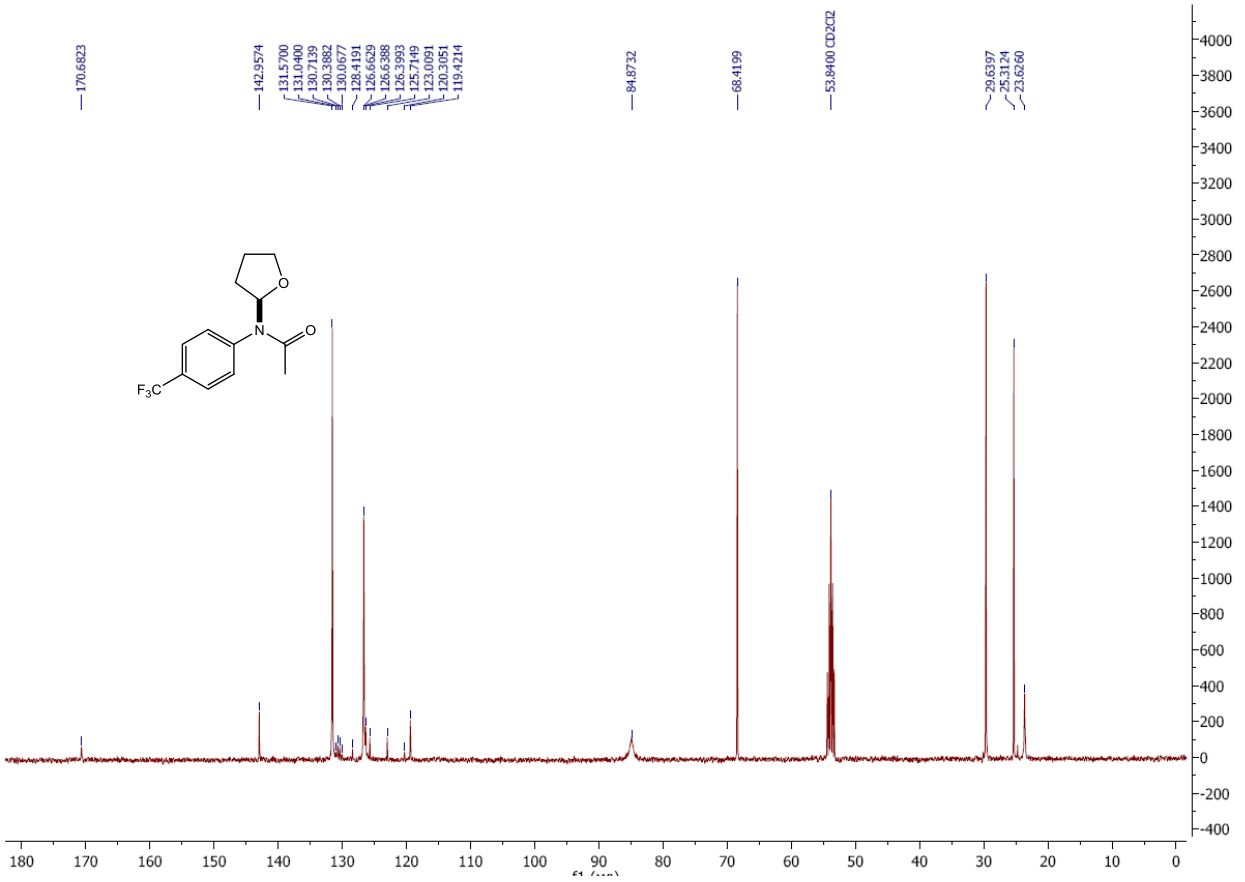
^{1}H and ^{13}C NMR spectra of N-(4-cyanophenyl)-N-(tetrahydrofuran-2-yl)acetamide (5j)



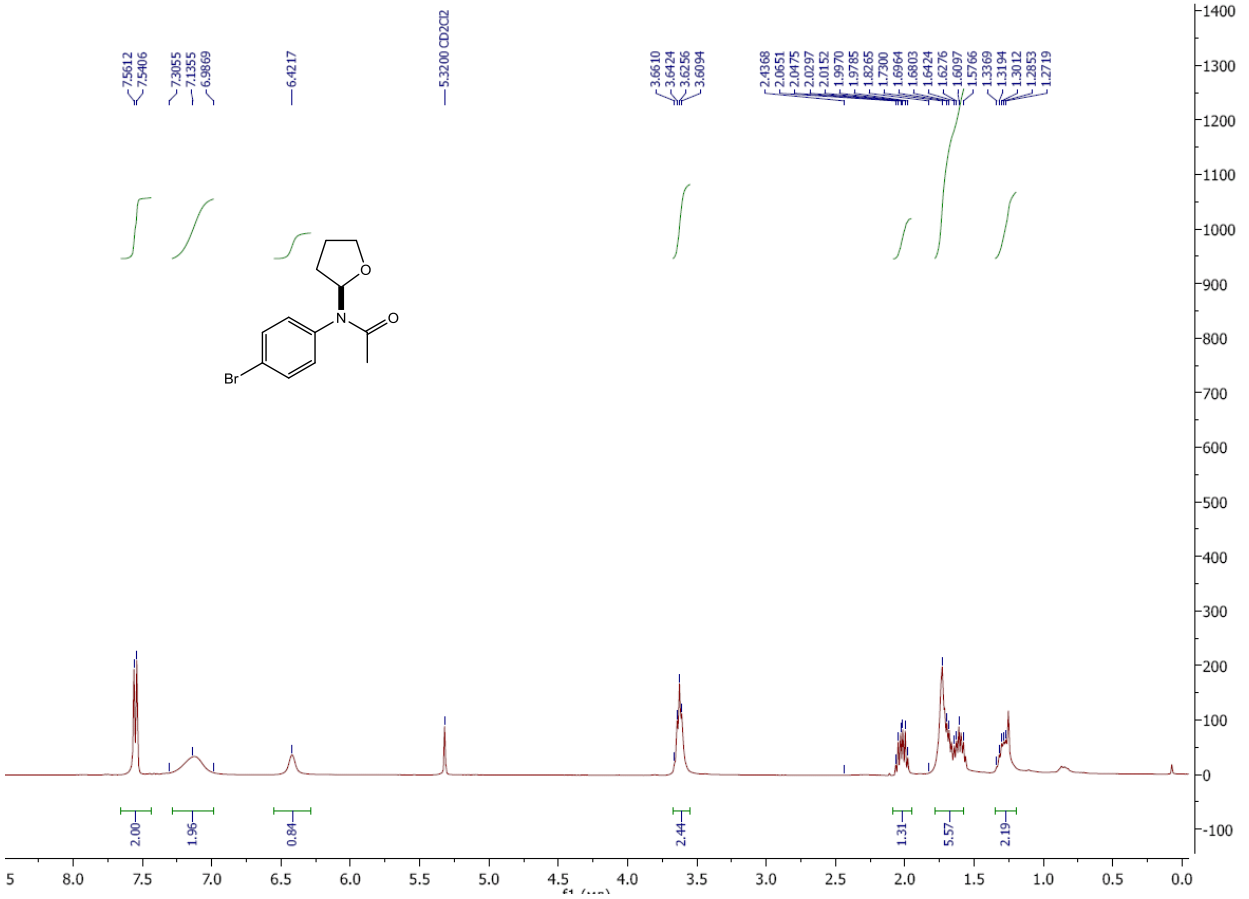


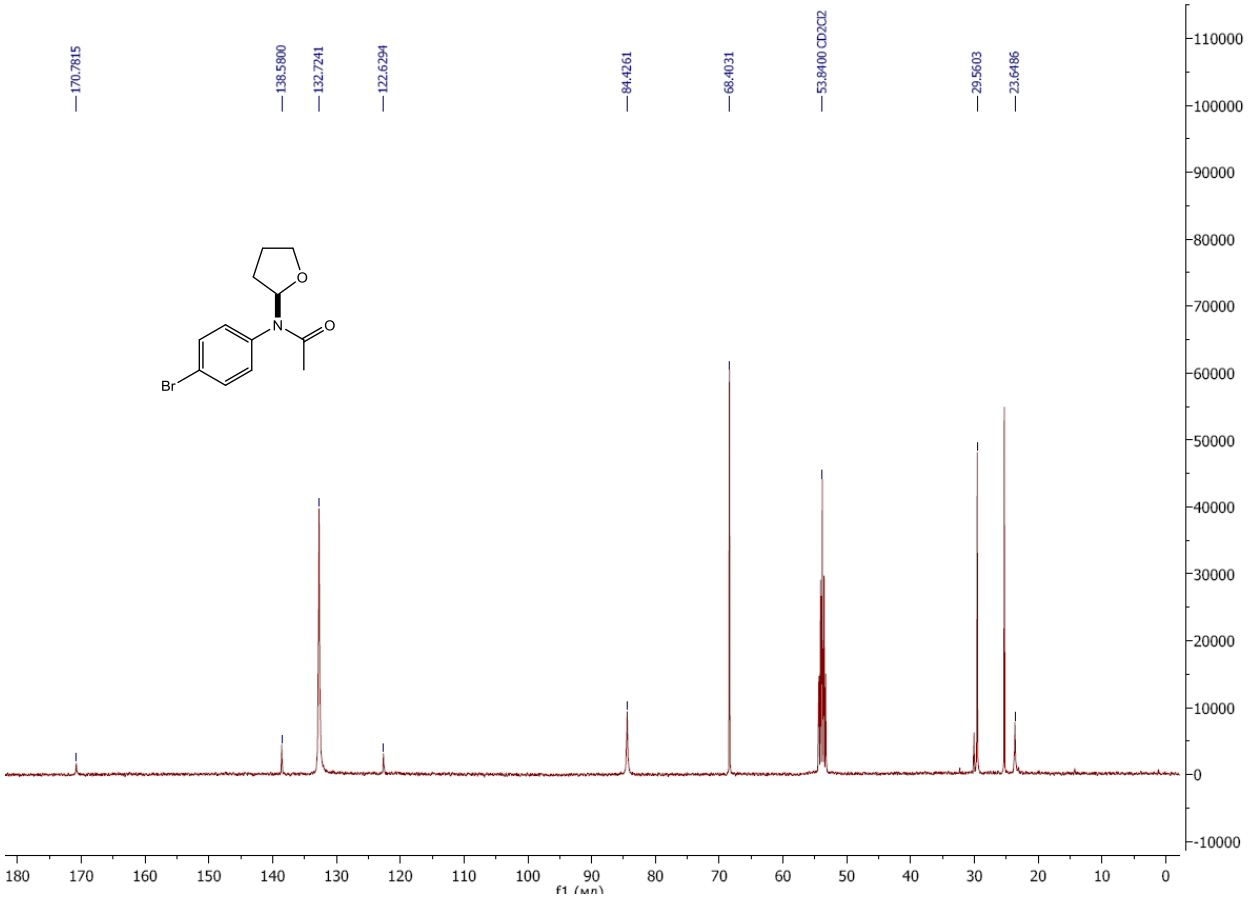
^{1}H and ^{13}C NMR spectra of N-(tetrahydrofuran-2-yl)-N-(4-(trifluoromethyl)phenyl)acetamide (5k)



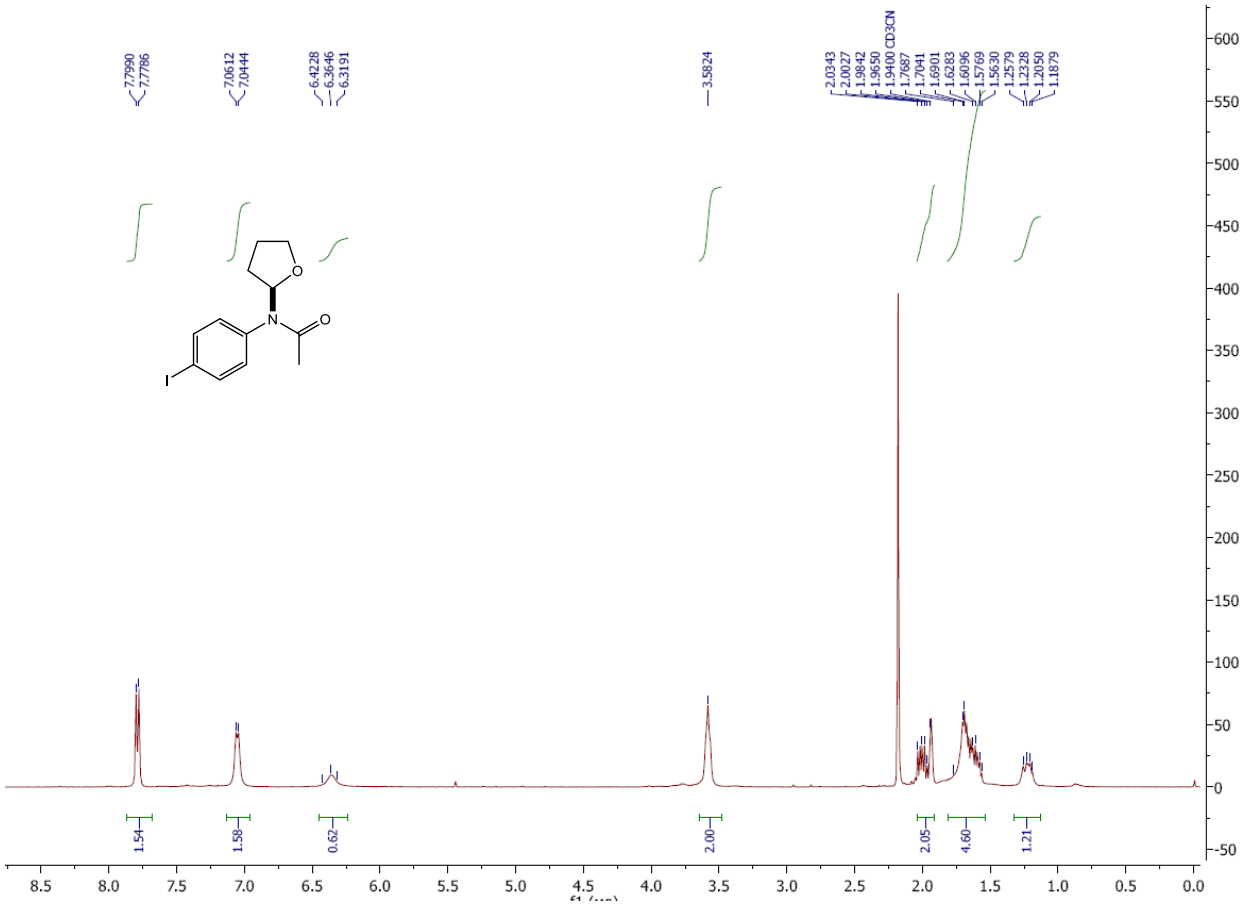


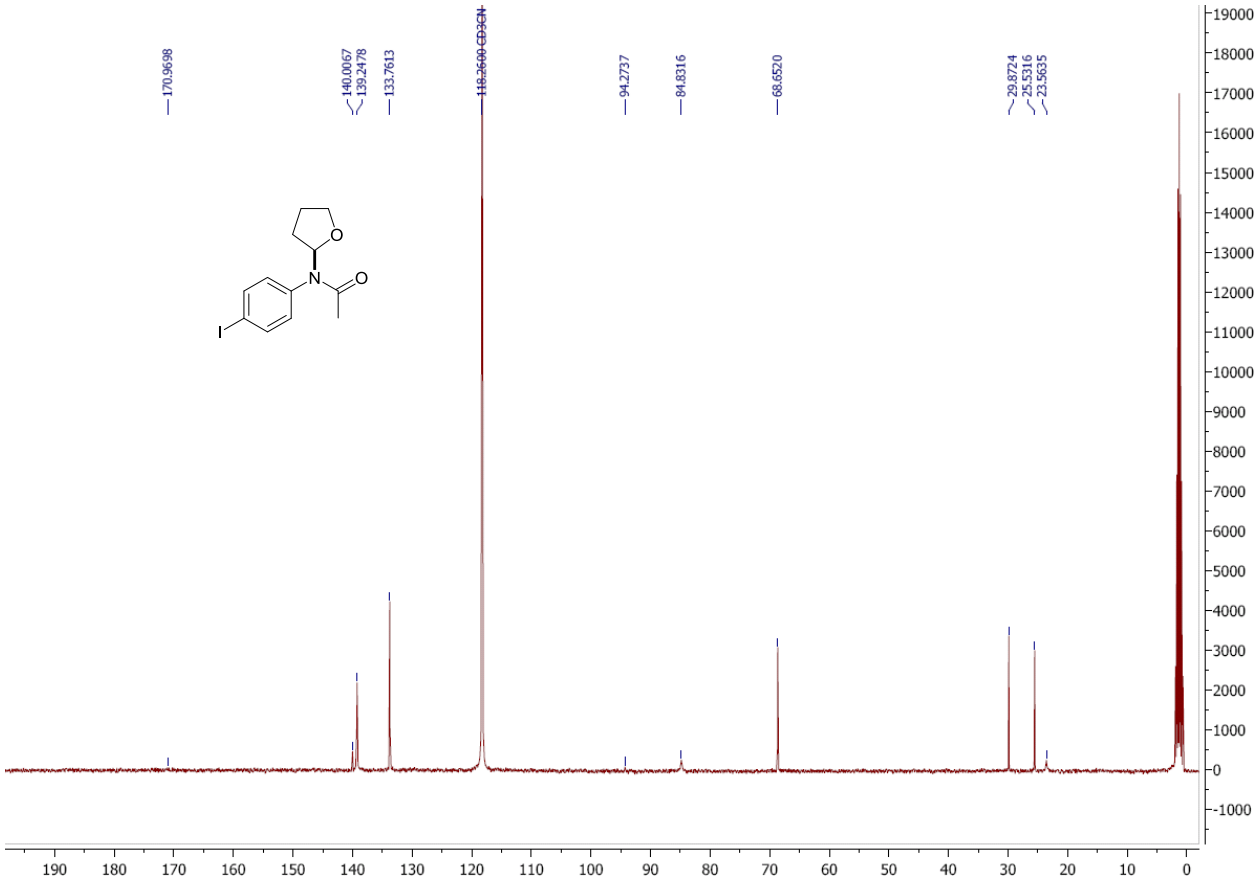
^{1}H and ^{13}C NMR spectra of N-(4-bromophenyl)-N-(tetrahydrofuran-2-yl)acetamide (5l)



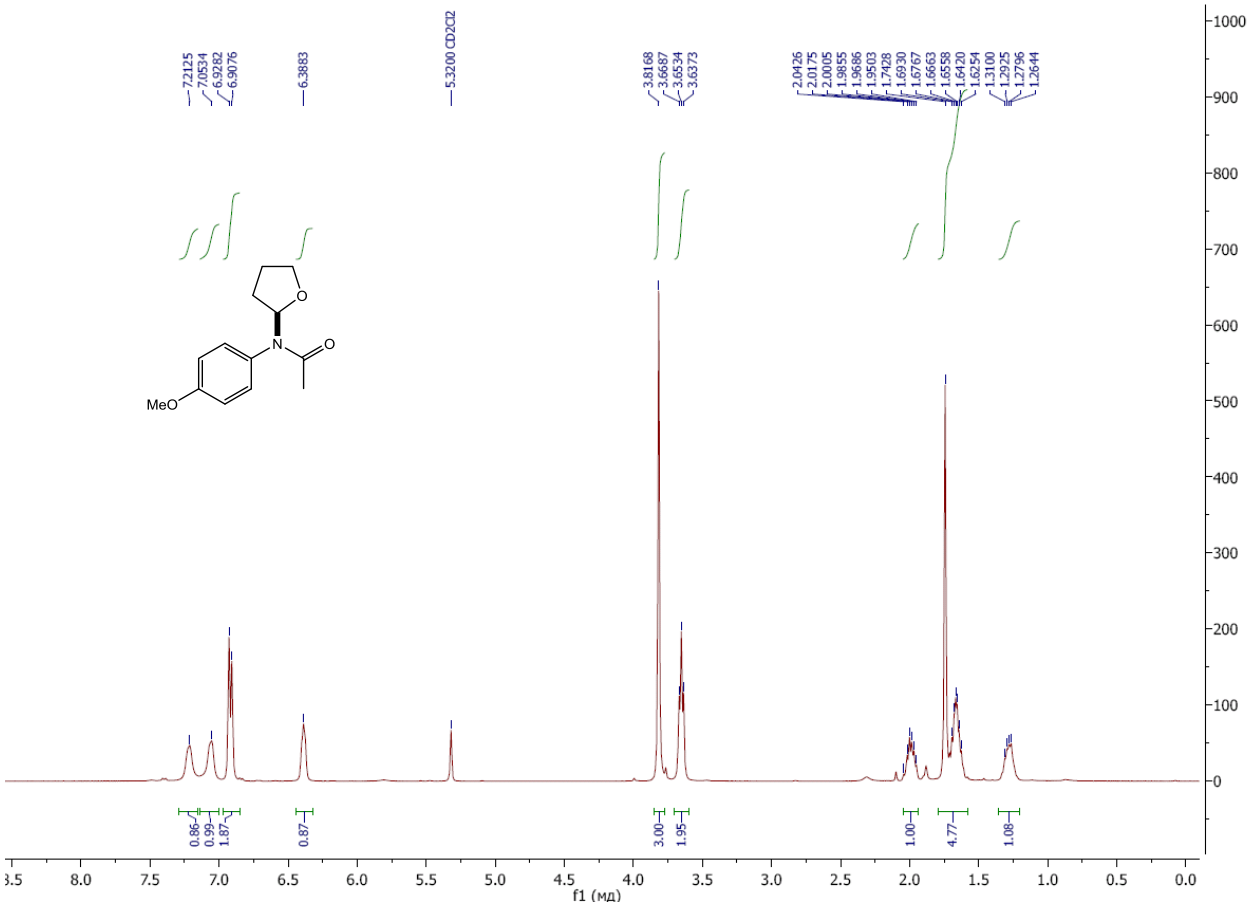


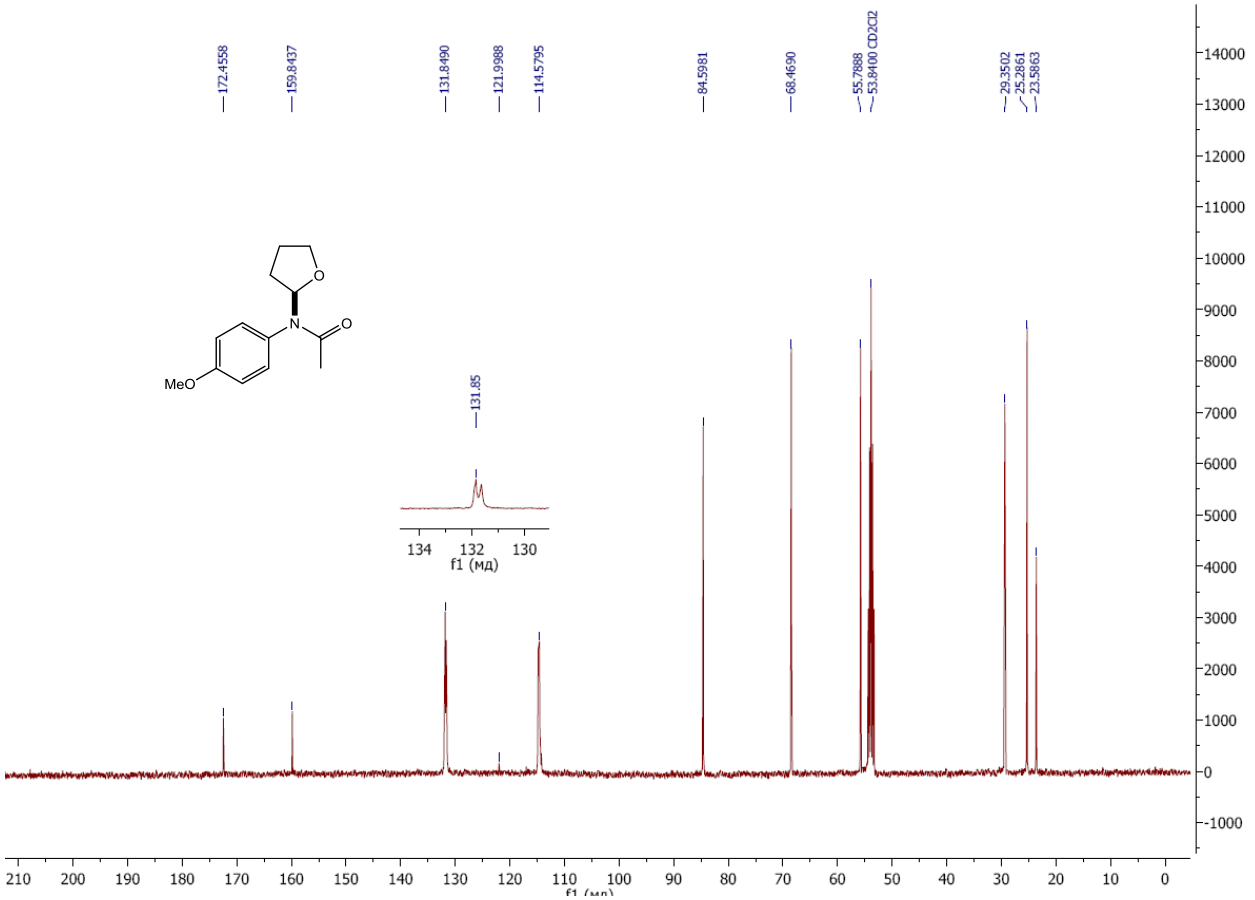
^{1}H and ^{13}C NMR spectra of N-(4-iodophenyl)-N-(tetrahydrofuran-2-yl)acetamide (5m)



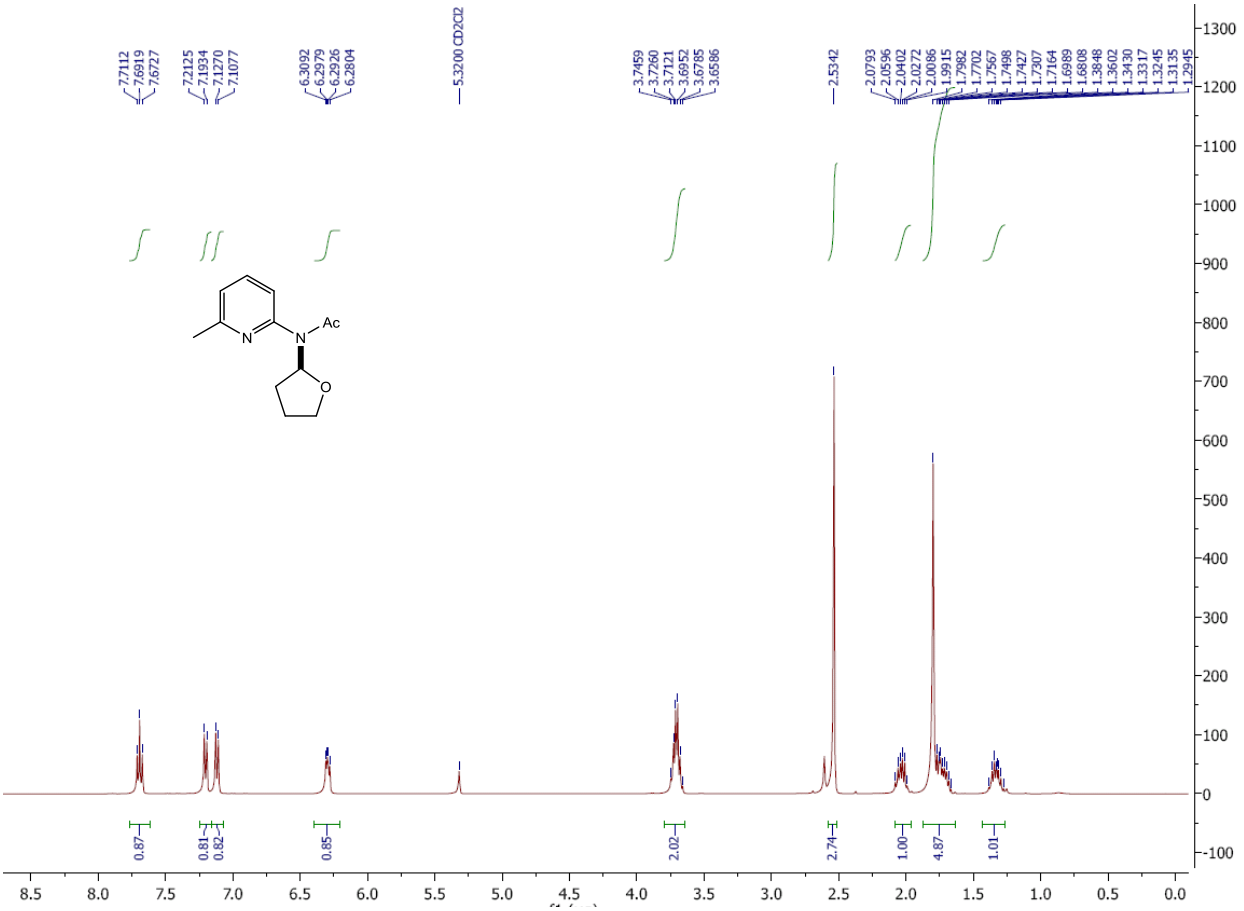


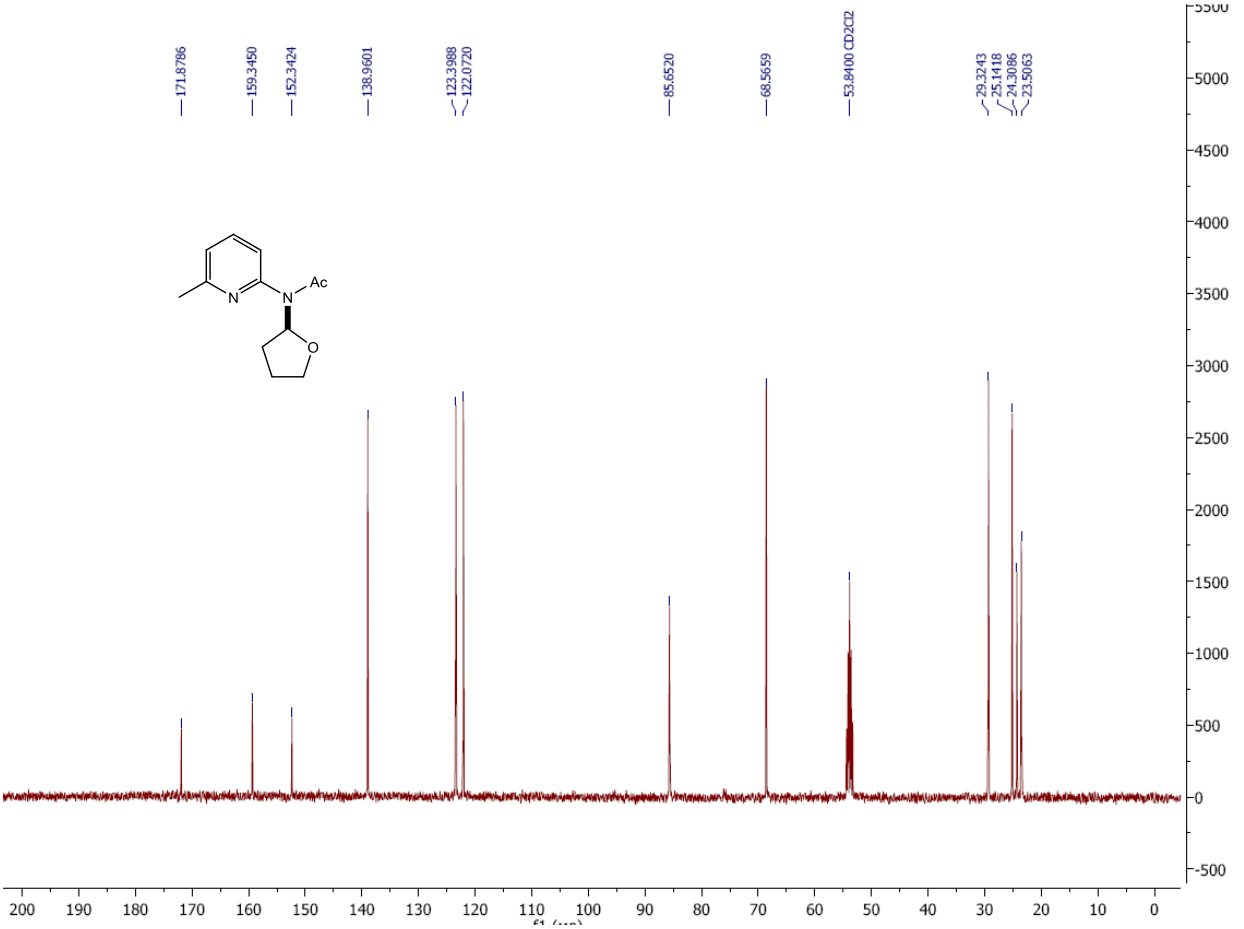
^{1}H and ^{13}C NMR spectra of N-(4-methoxyphenyl)-N-(tetrahydrofuran-2-yl)acetamide (5n)



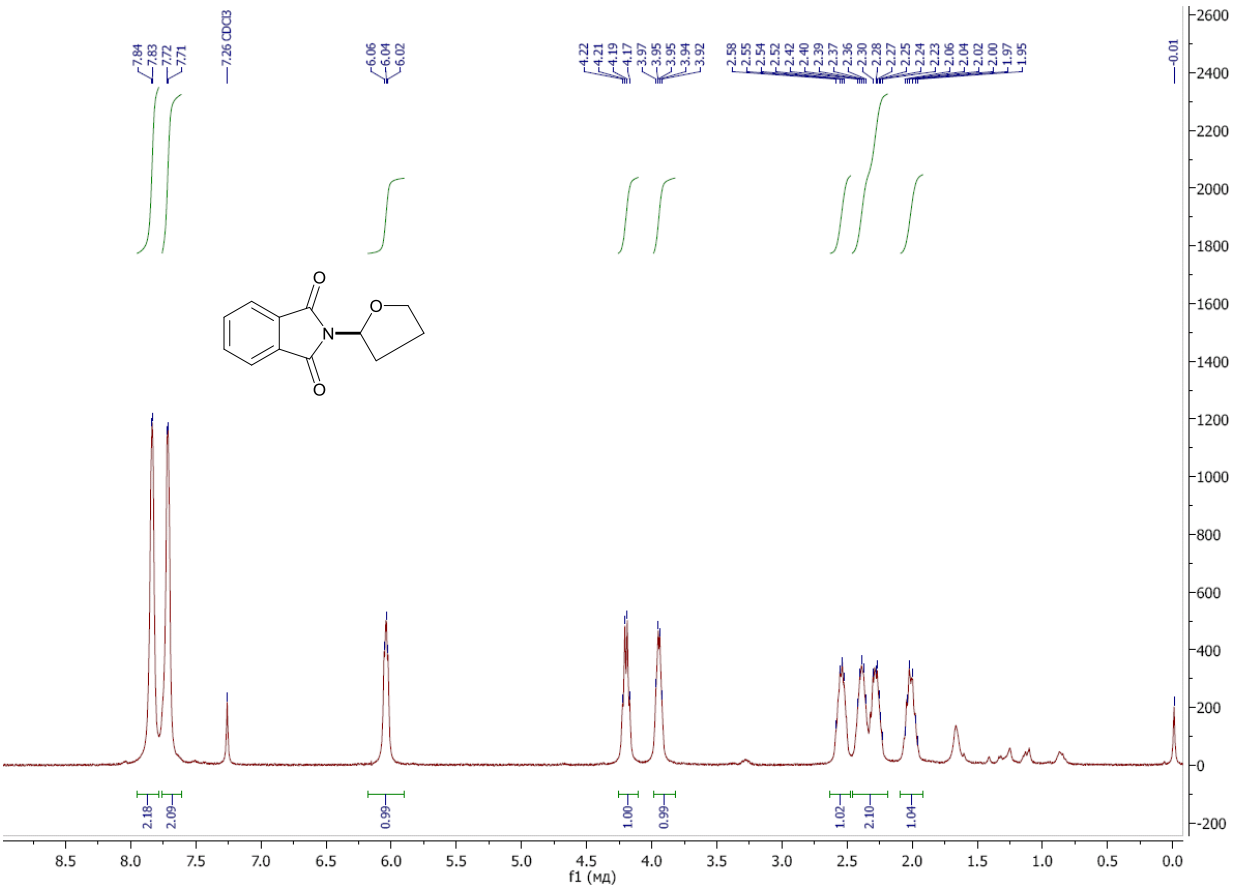


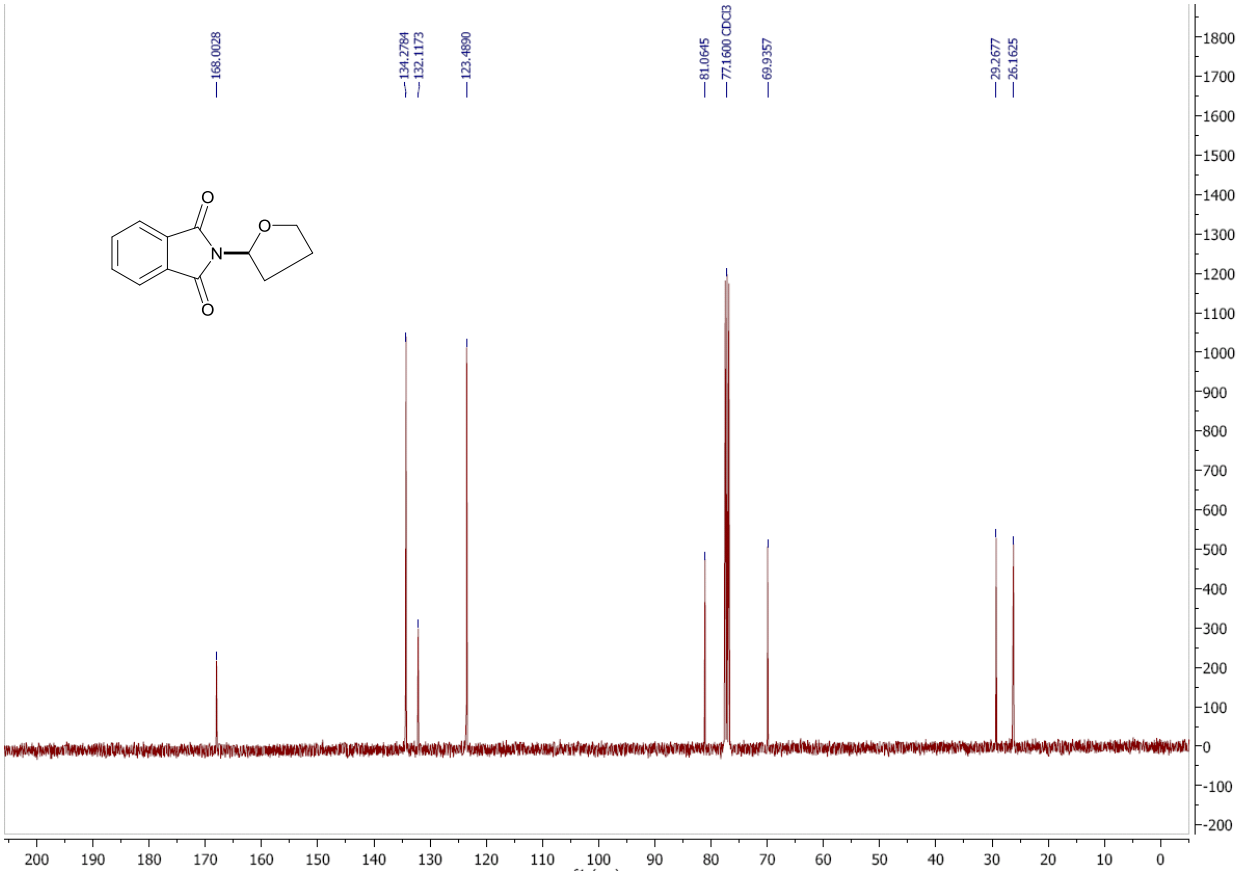
^{1}H and ^{13}C NMR spectra of N-(6-methylpyridin-2-yl)-N-(tetrahydrofuran-2-yl)acetamide (5o)



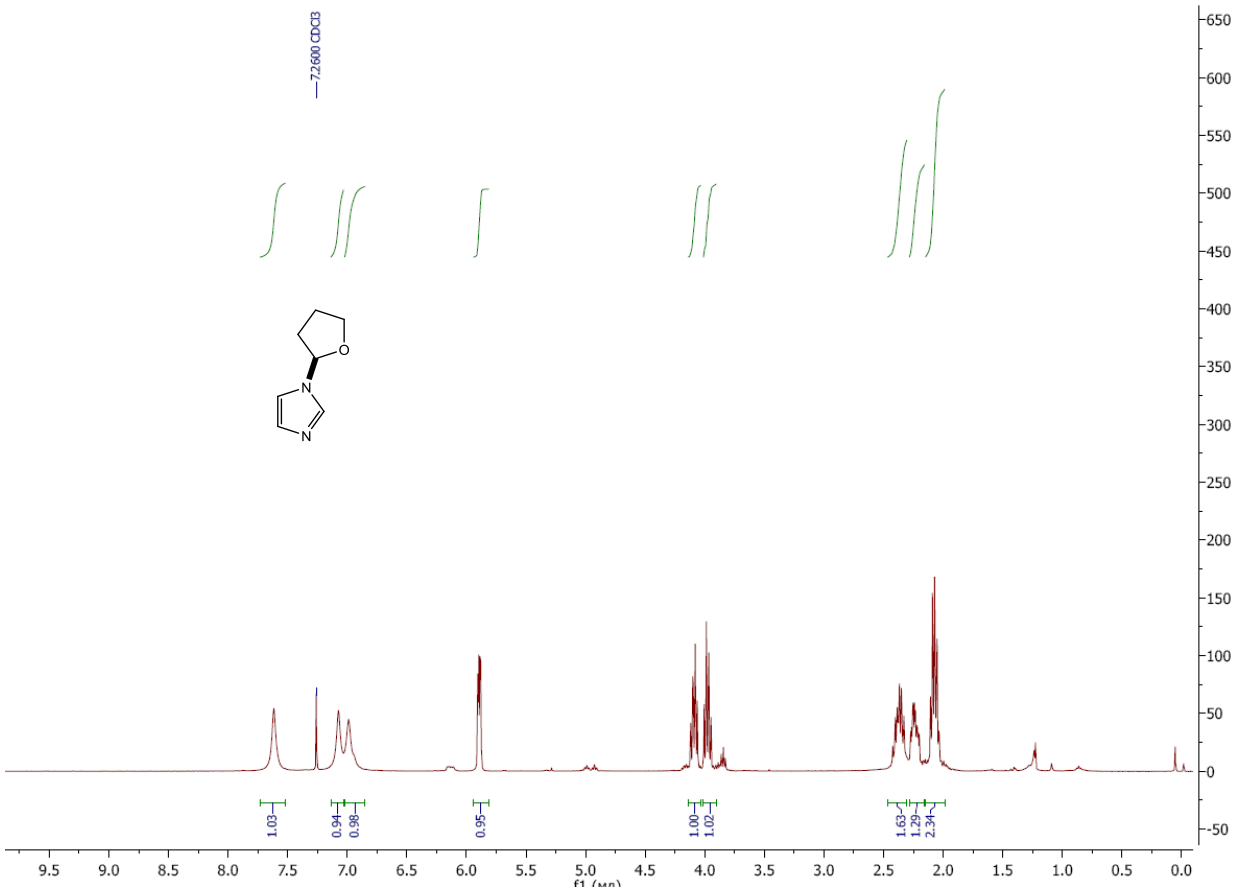


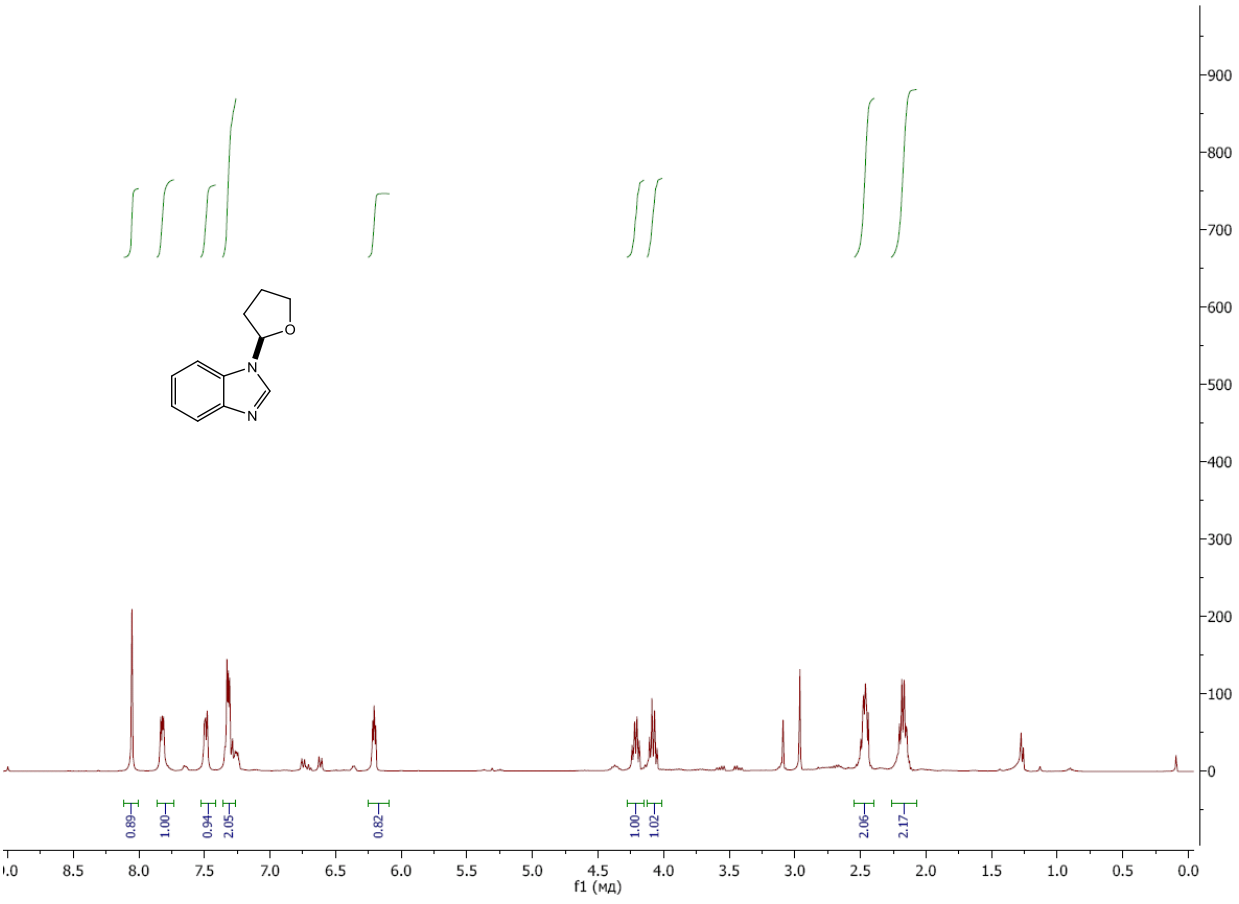
^{1}H and ^{13}C NMR spectra of 2-(tetrahydrofuran-2-yl)isoindoline-1,3-dione (5p)



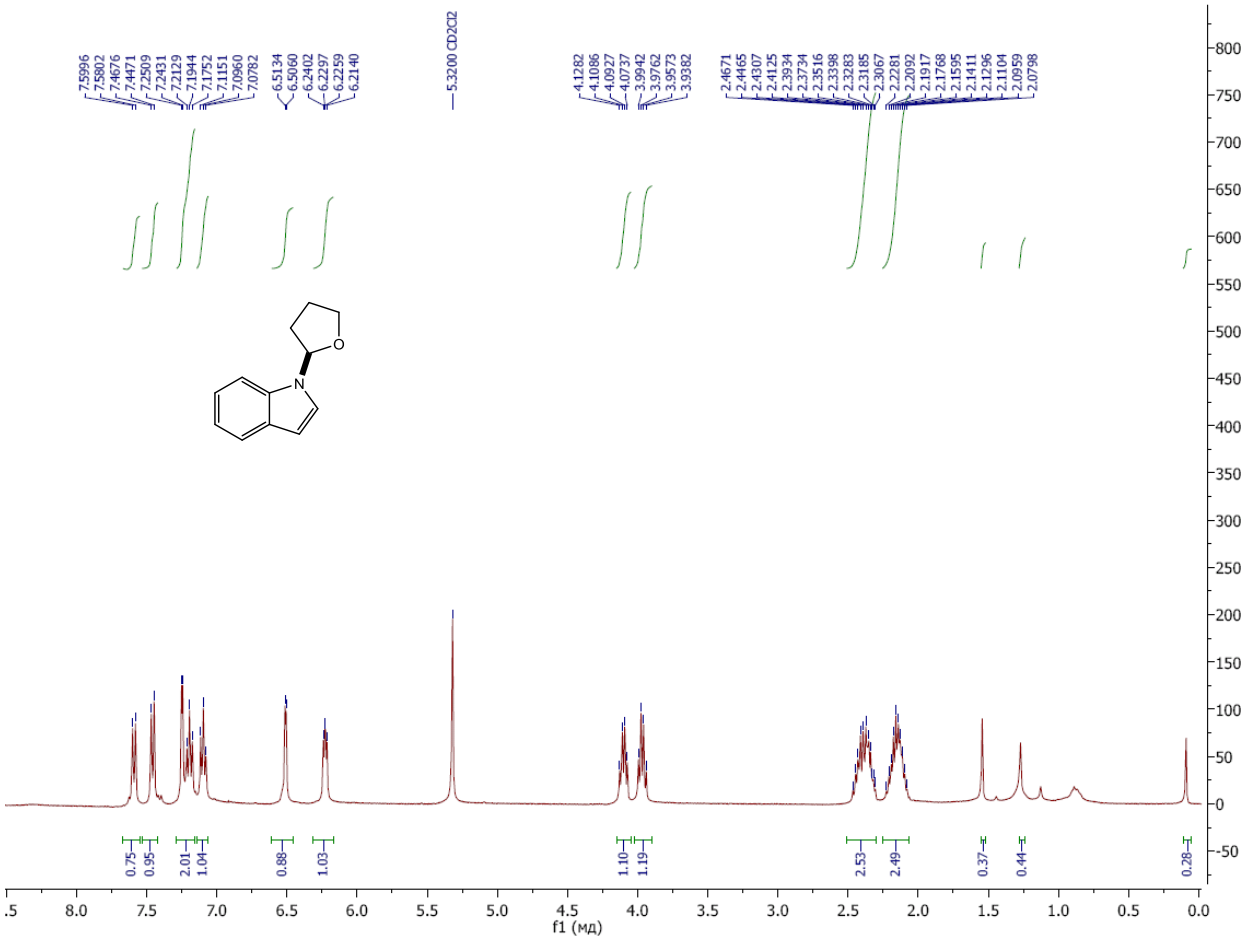


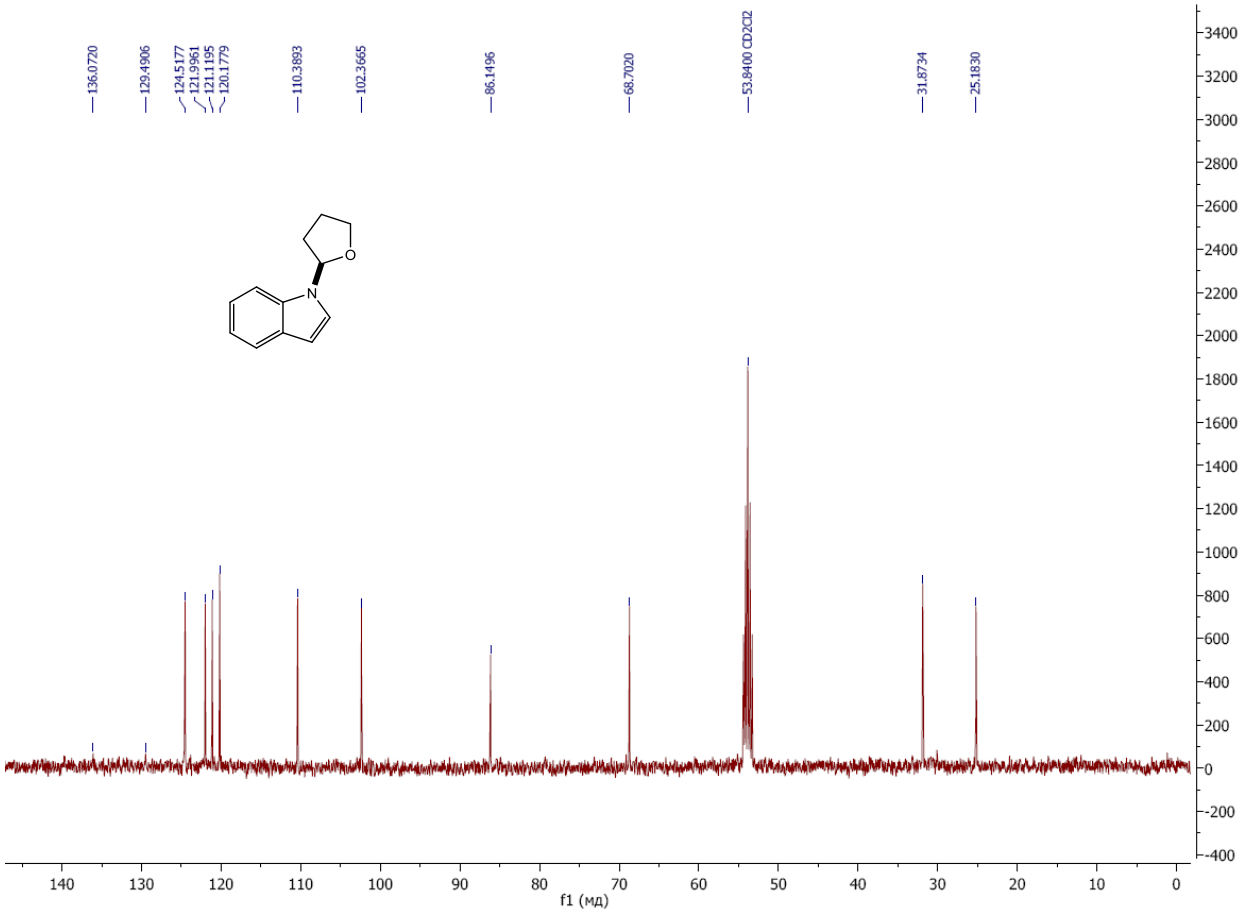
^{1}H NMR spectra of 1-(Tetrahydrofuran-2-yl)-1*H*-imidazole 7(a) and 1-(Tetrahydrofuran-2-yl)-1*H*-benzo[d]imidazole (7b)



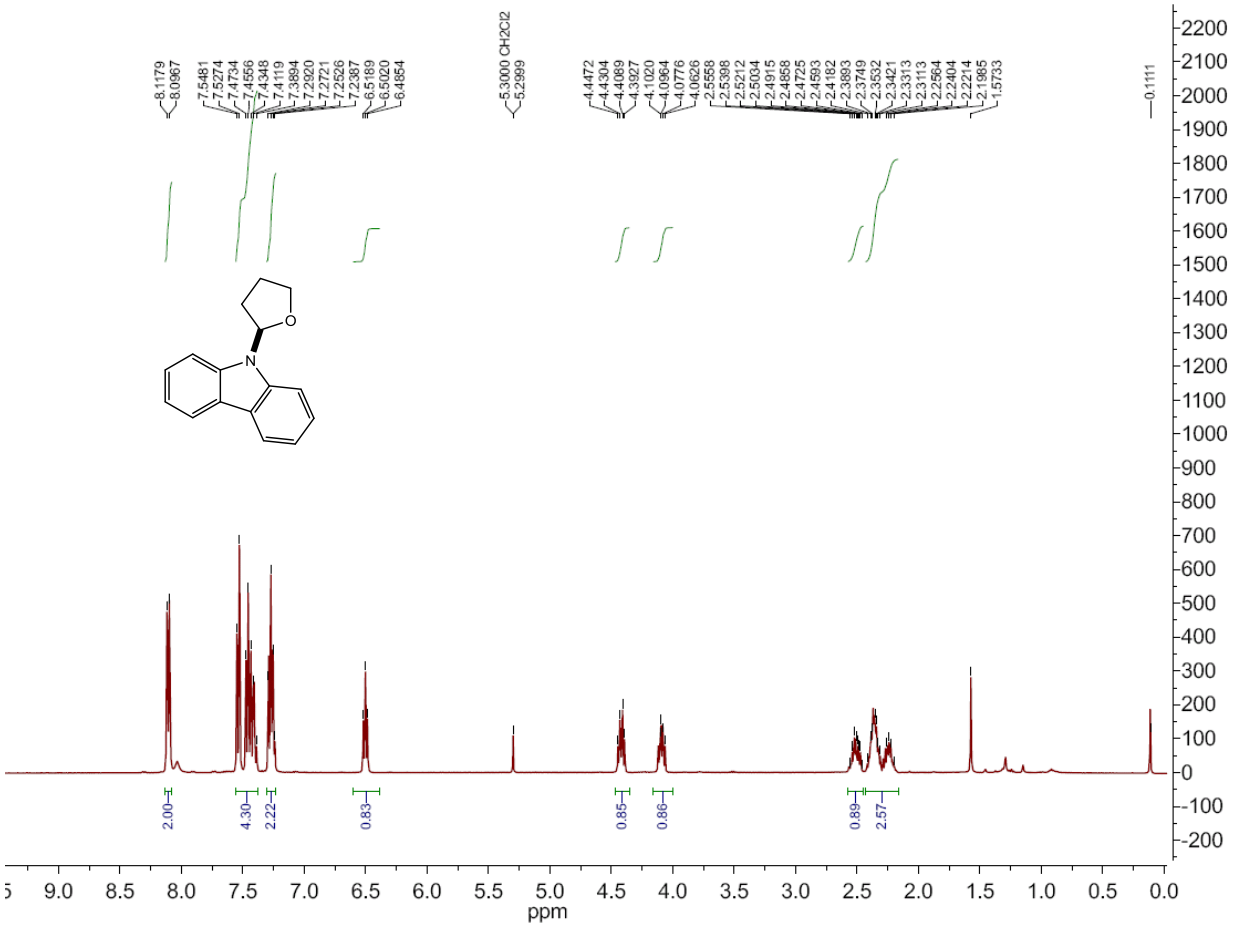


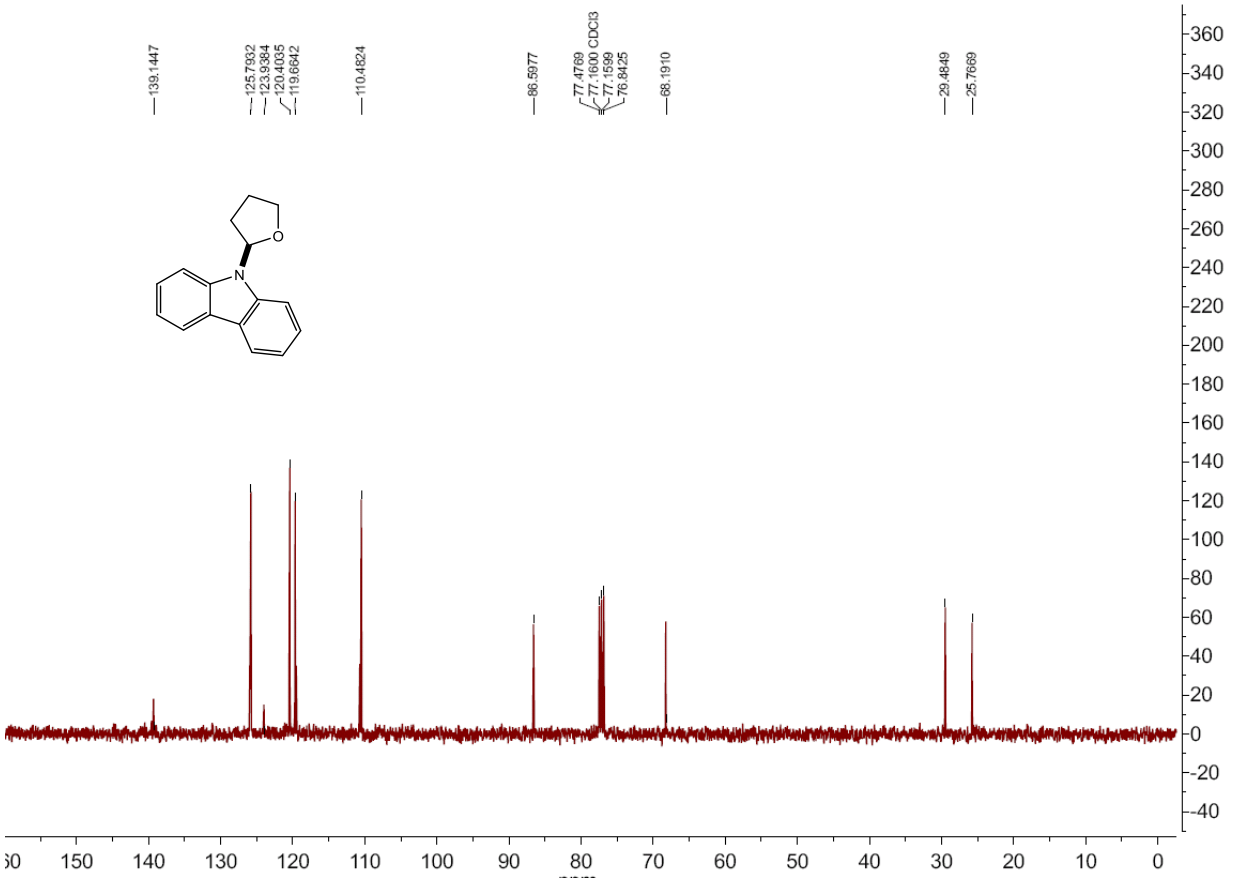
^{1}H and ^{13}C NMR spectra of N-[Tetrahydrofuran-2-yl]-1H-indole (7c)



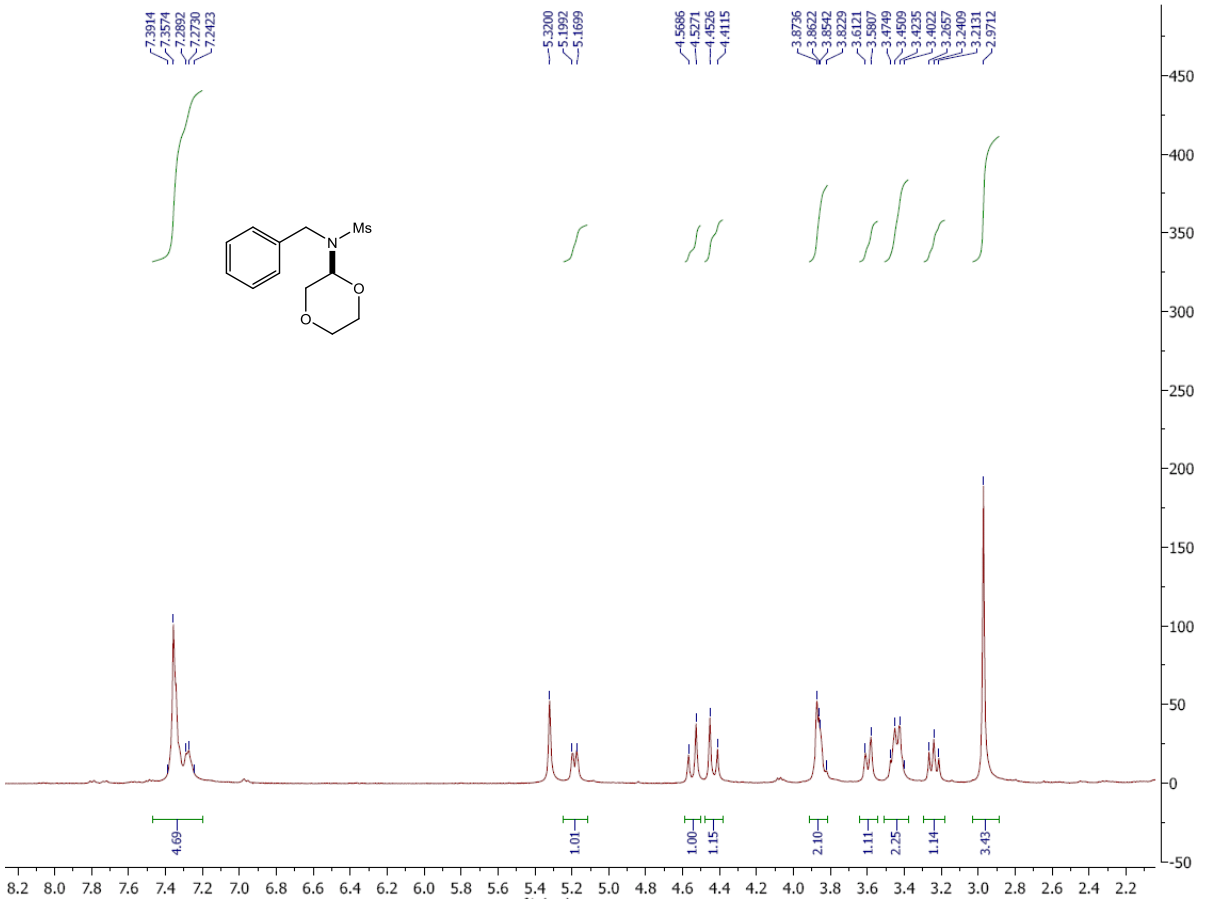


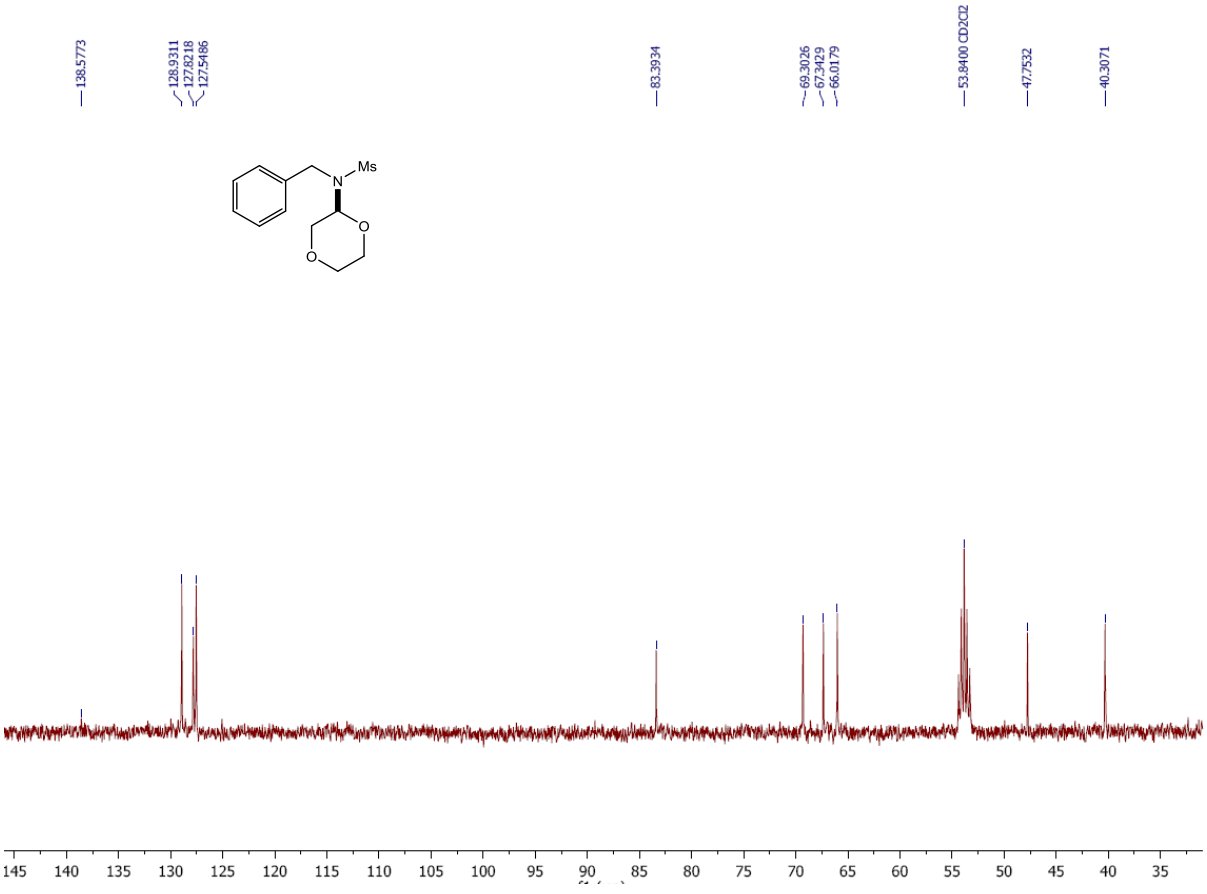
^{1}H and ^{13}C NMR spectra of 9-(tetrahydrofuran-2-yl)-9H-carbazole (7d)



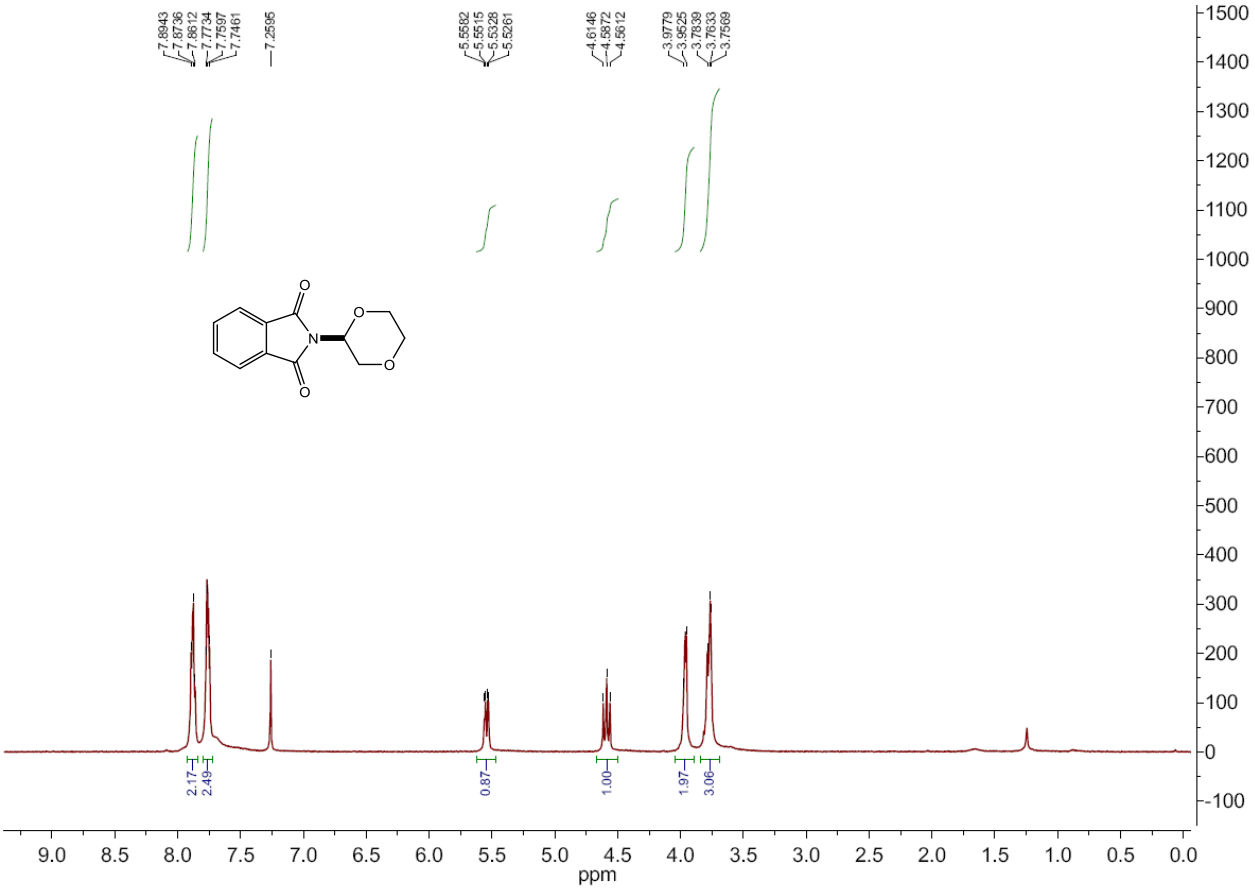


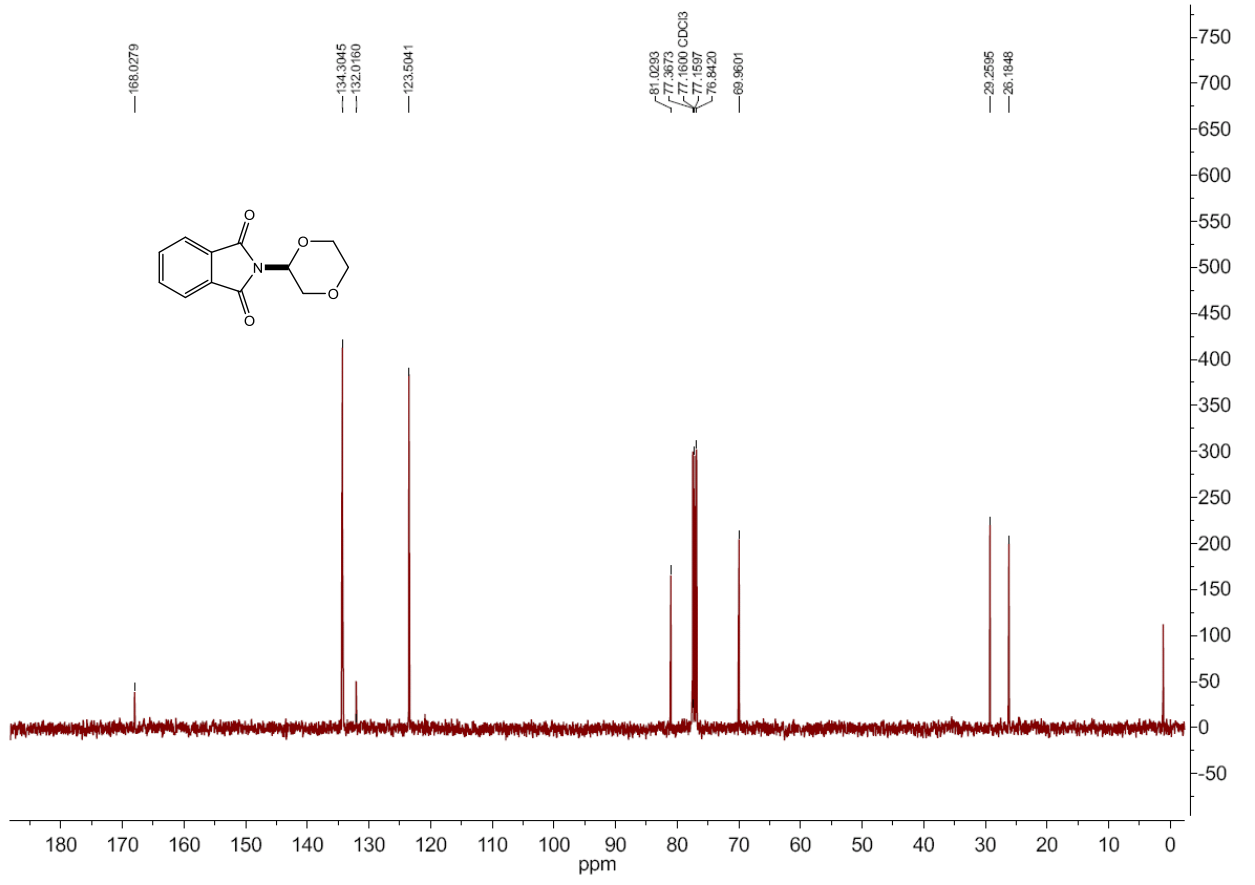
^{1}H and ^{13}C NMR spectra of N-benzyl-N-(1,4-dioxan-2-yl)methanesulfonamide (8a)



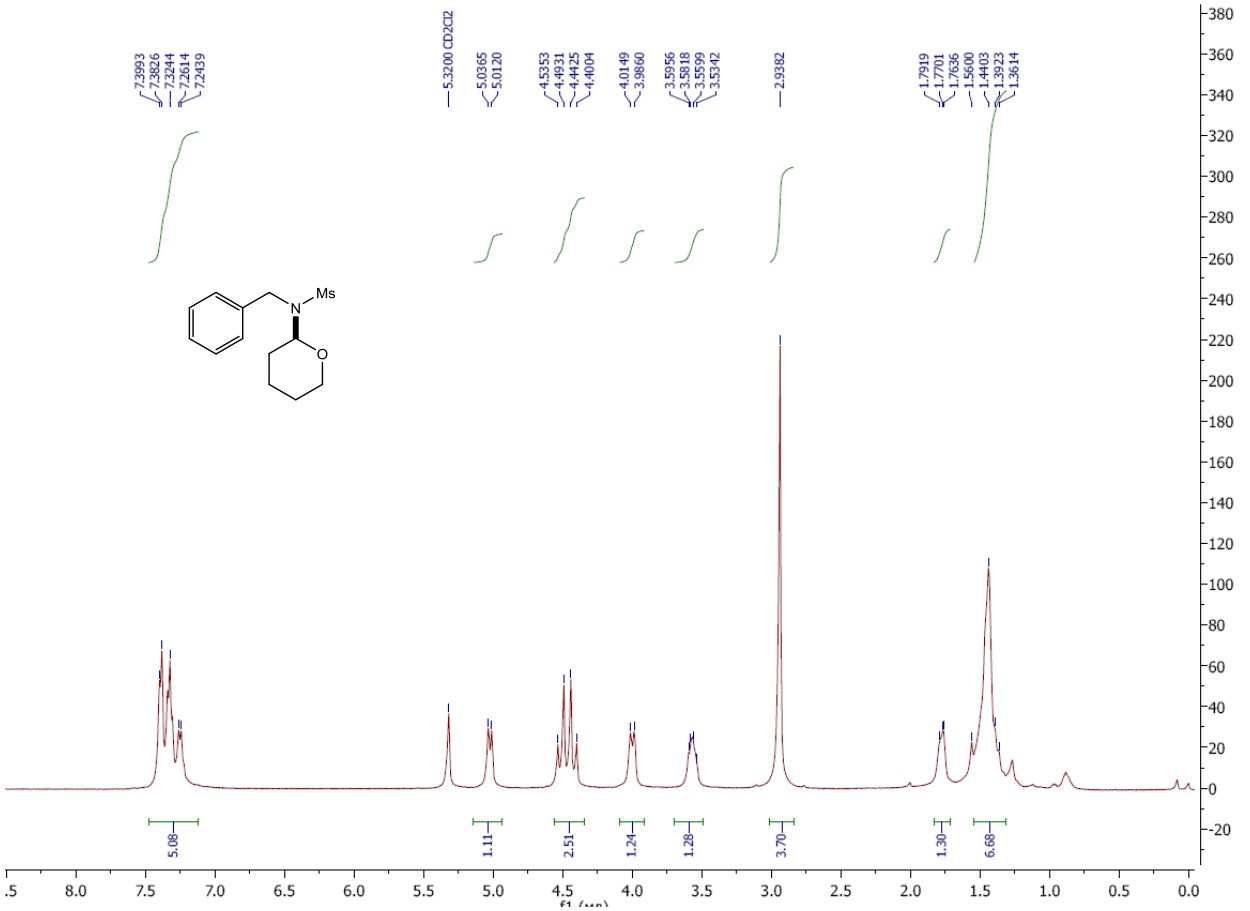


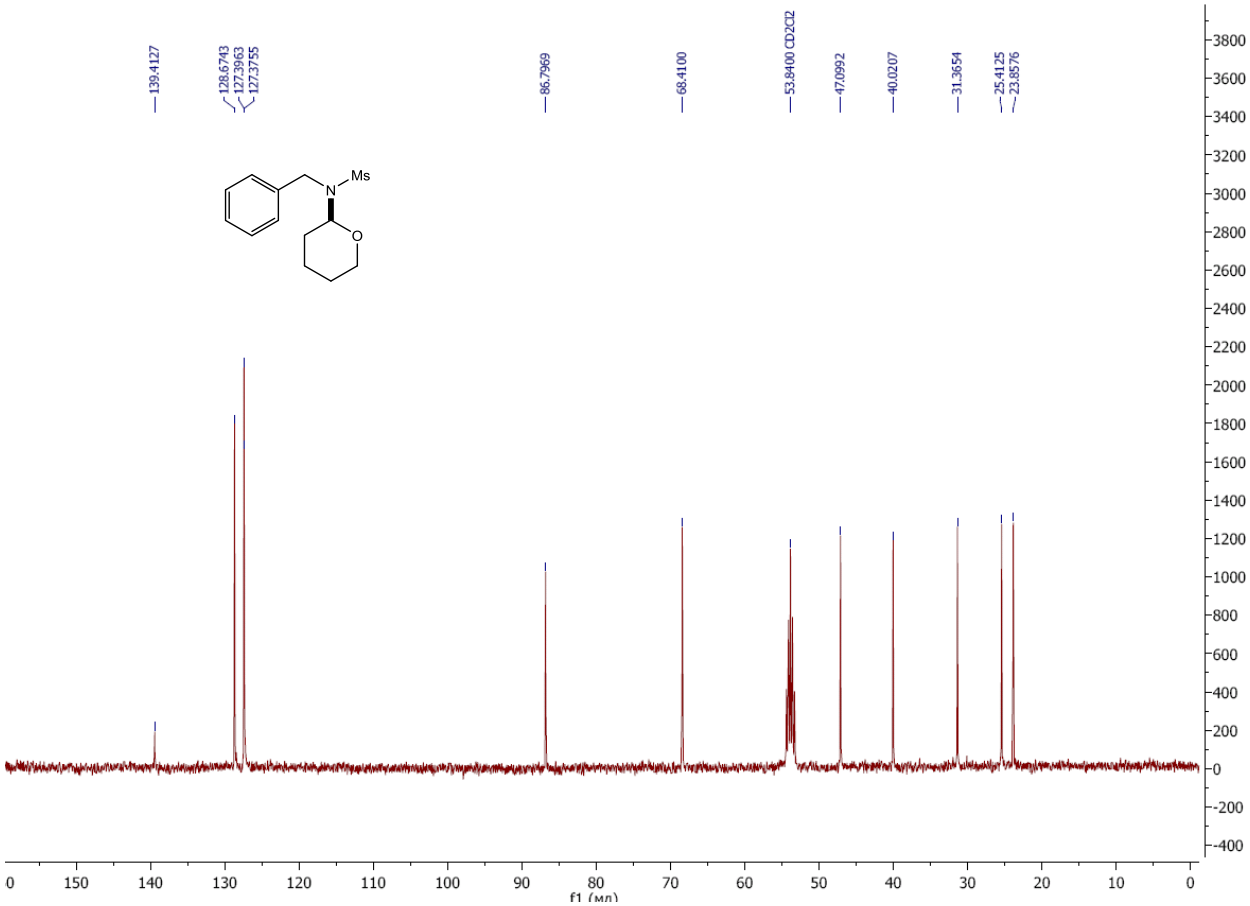
^{1}H and ^{13}C NMR spectra of 2-(1,4-dioxan-2-yl)isoindoline-1,3-dione (8b)



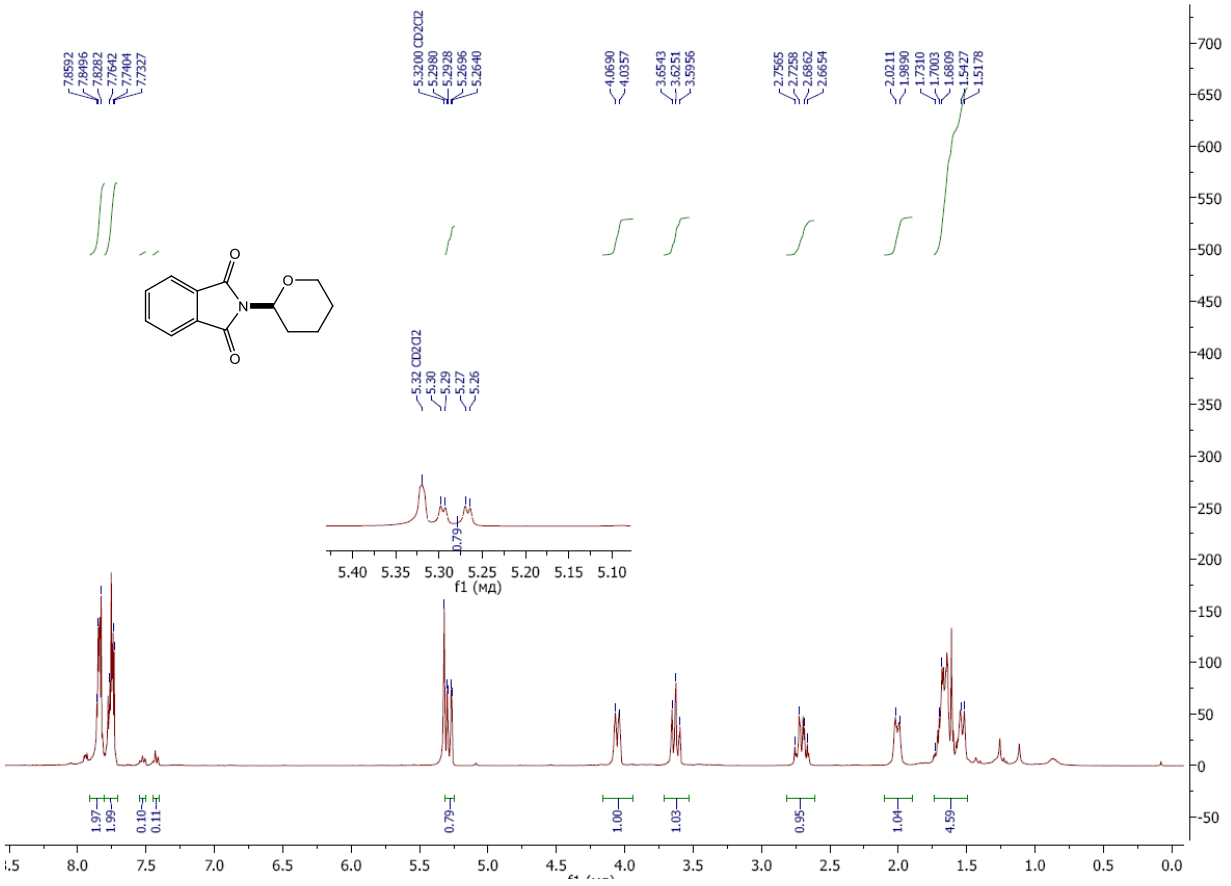


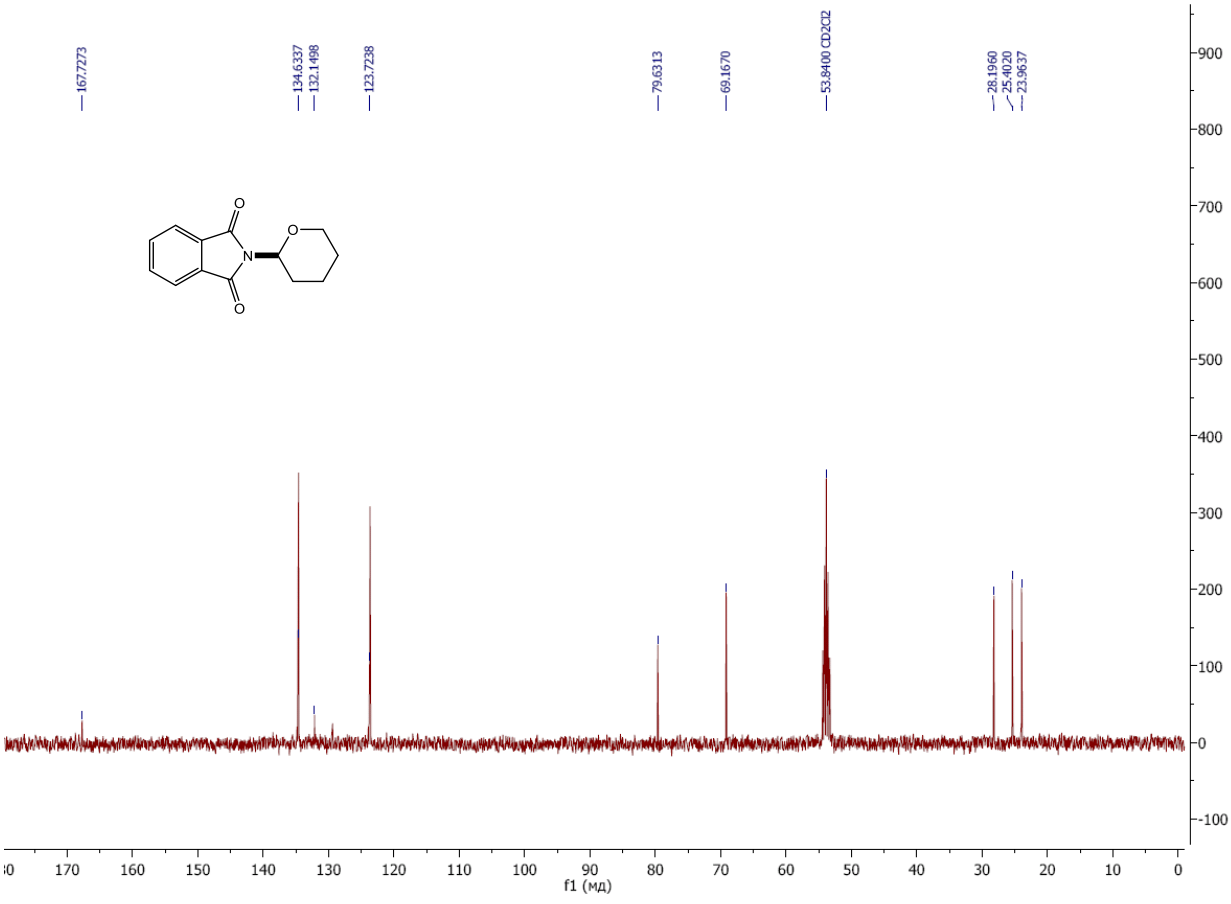
^{1}H and ^{13}C NMR spectra of N-benzyl-N-(tetrahydro-2H-pyran-2-yl)methanesulfonamide (8c)



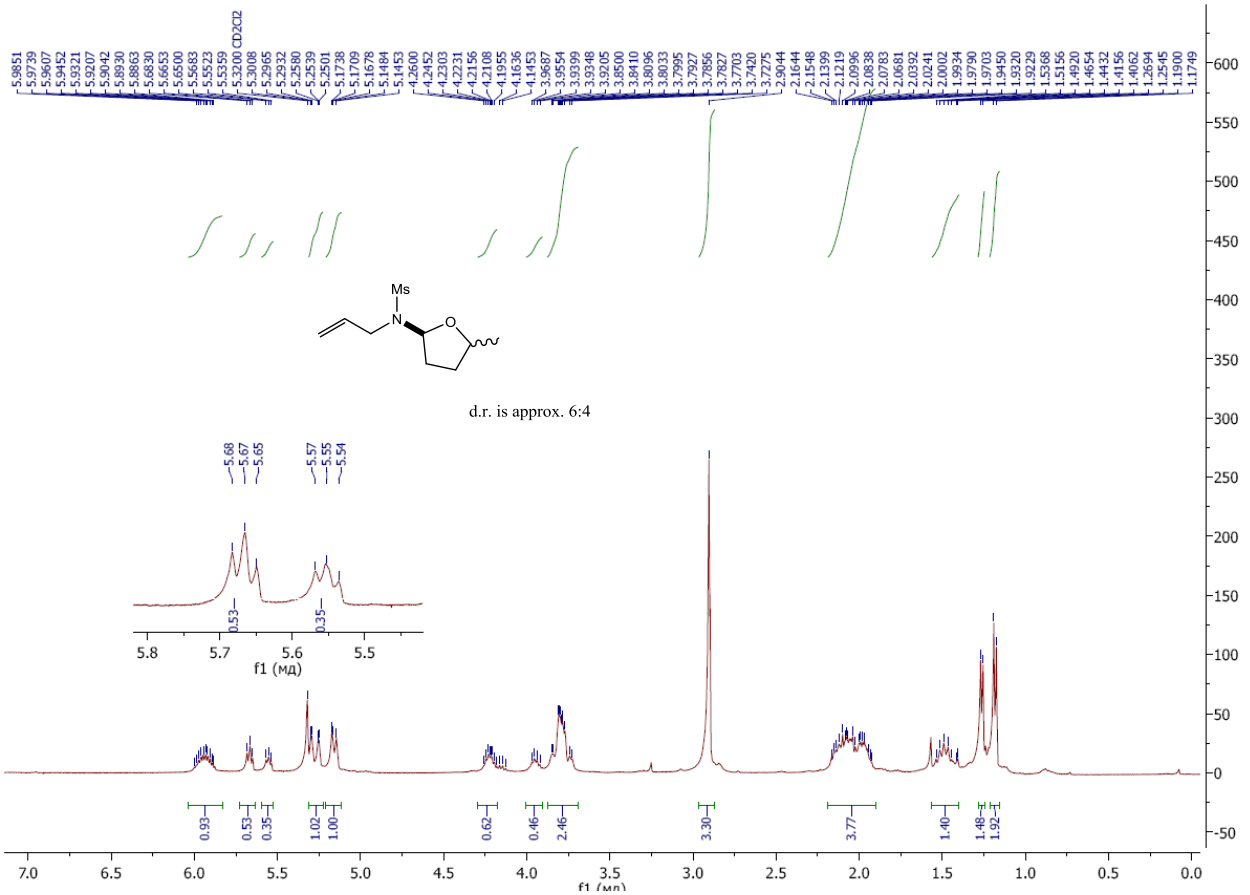


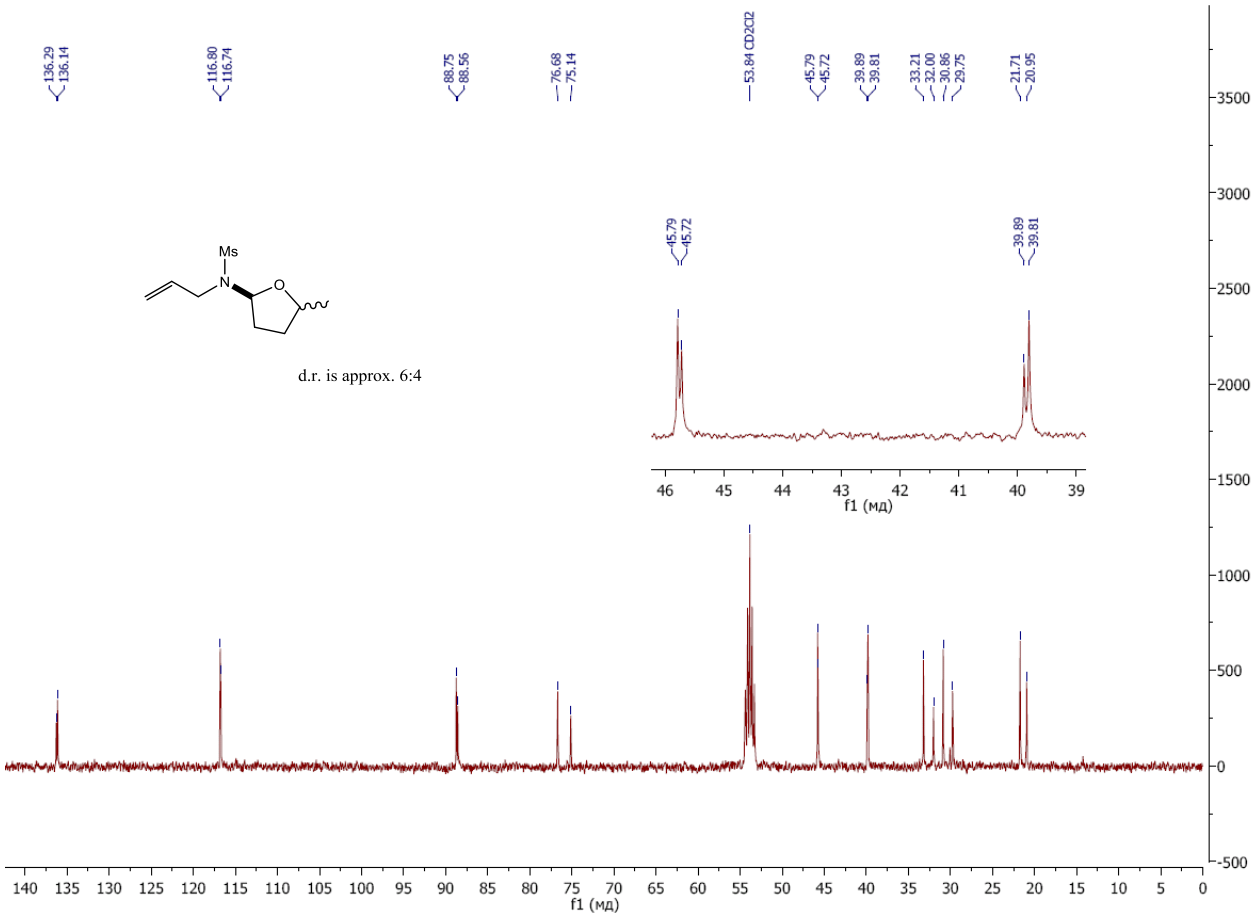
^{1}H and ^{13}C NMR spectra of 2-(tetrahydro-2H-pyran-2-yl)isoindoline-1,3-dione (8d)



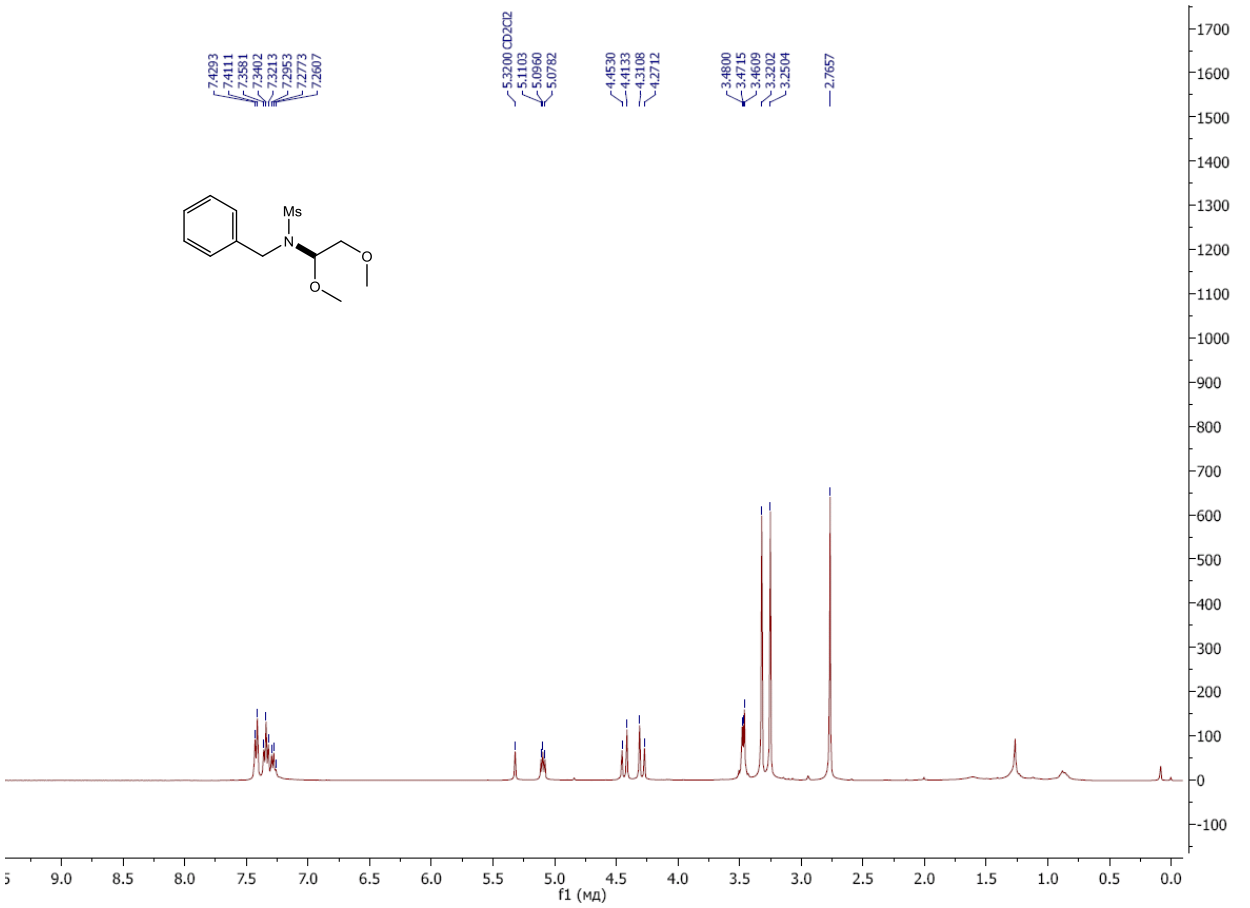


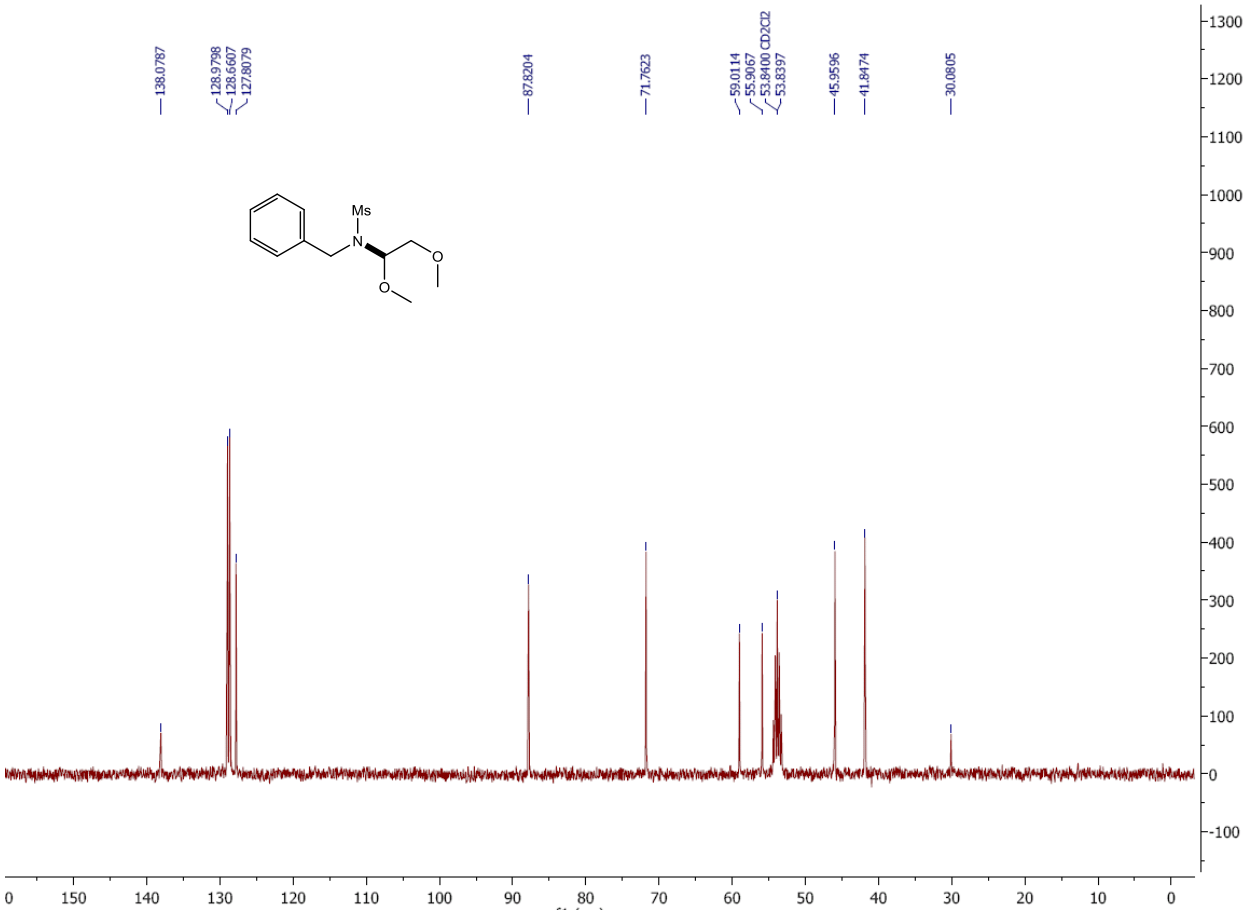
^{1}H and ^{13}C NMR spectra of N-allyl-N-(5-methyltetrahydrofuran-2-yl)methanesulfonamide (8e)



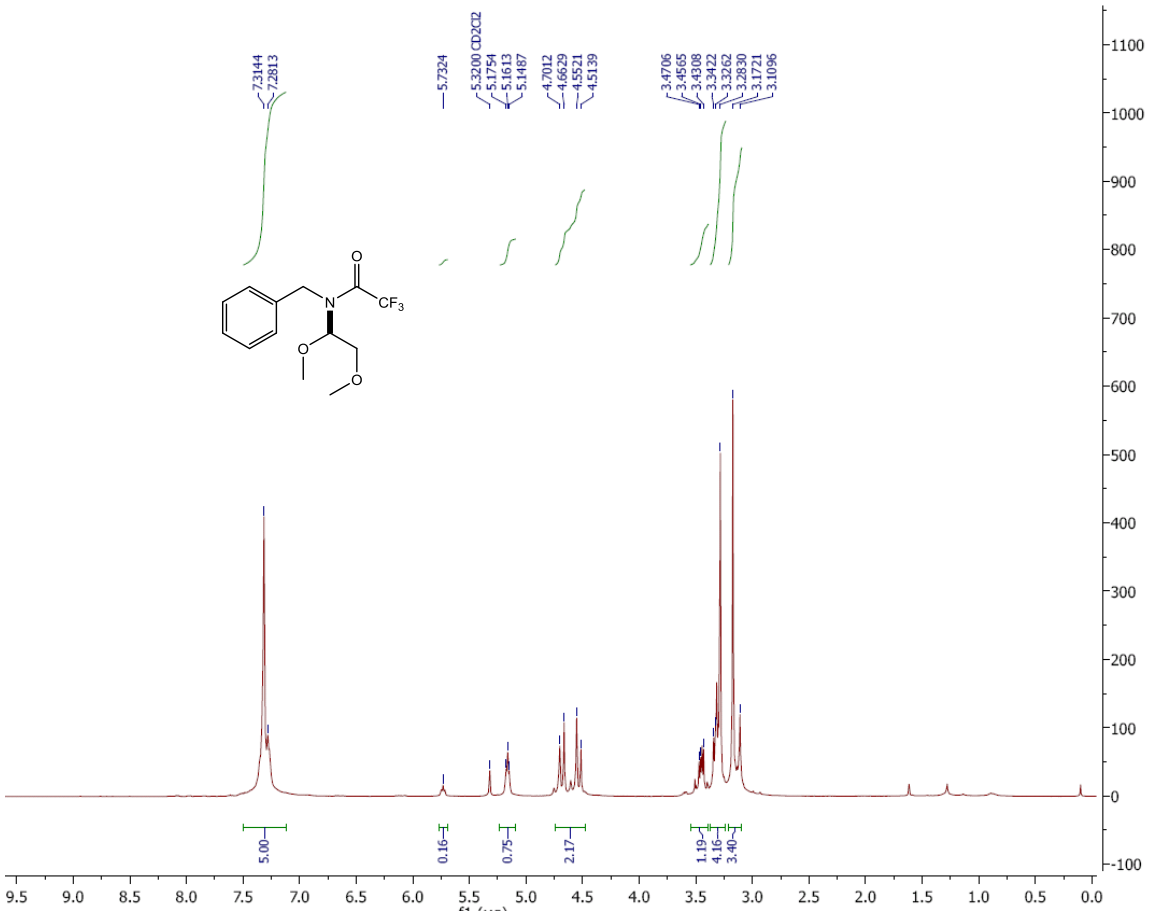


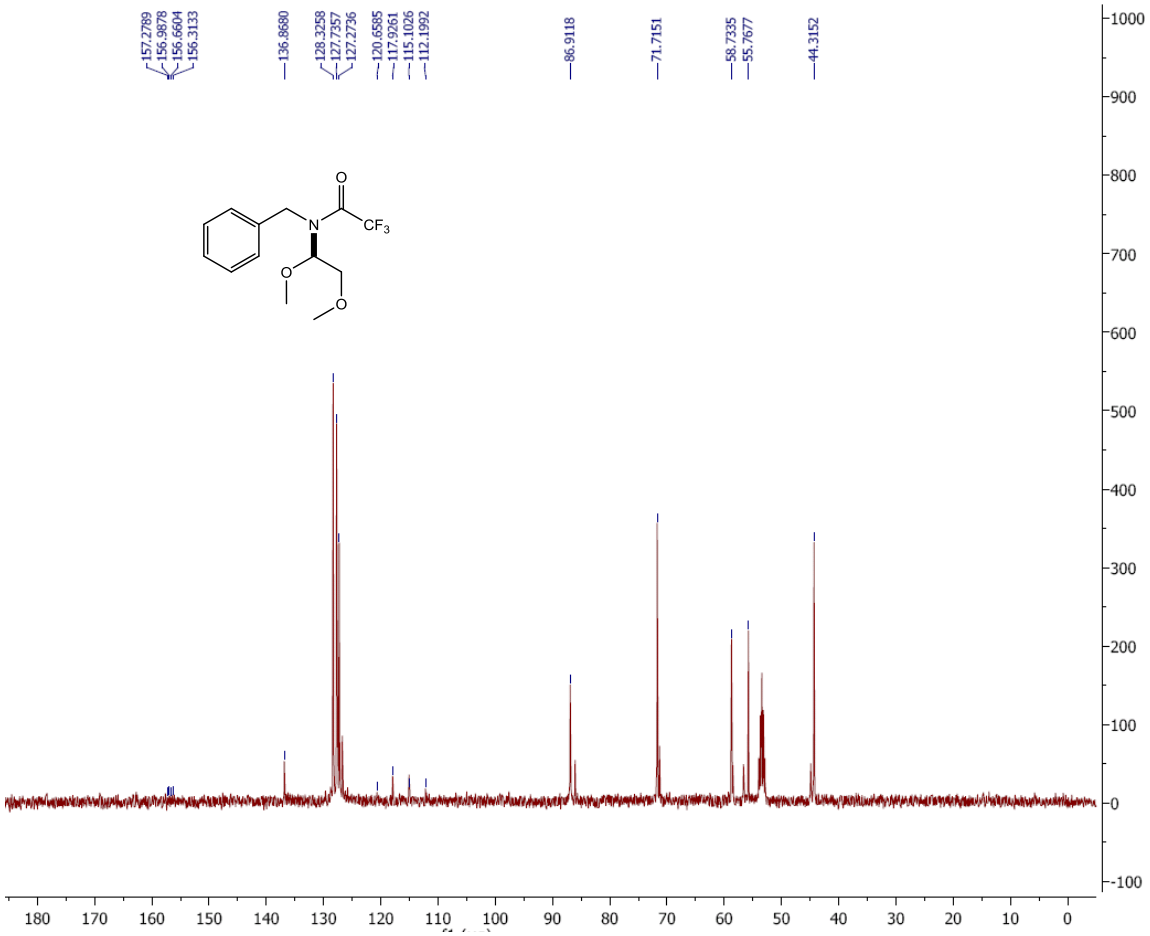
^{1}H and ^{13}C NMR spectra of N-benzyl-N-(1,2-dimethoxyethyl)methanesulfonamide (8f)



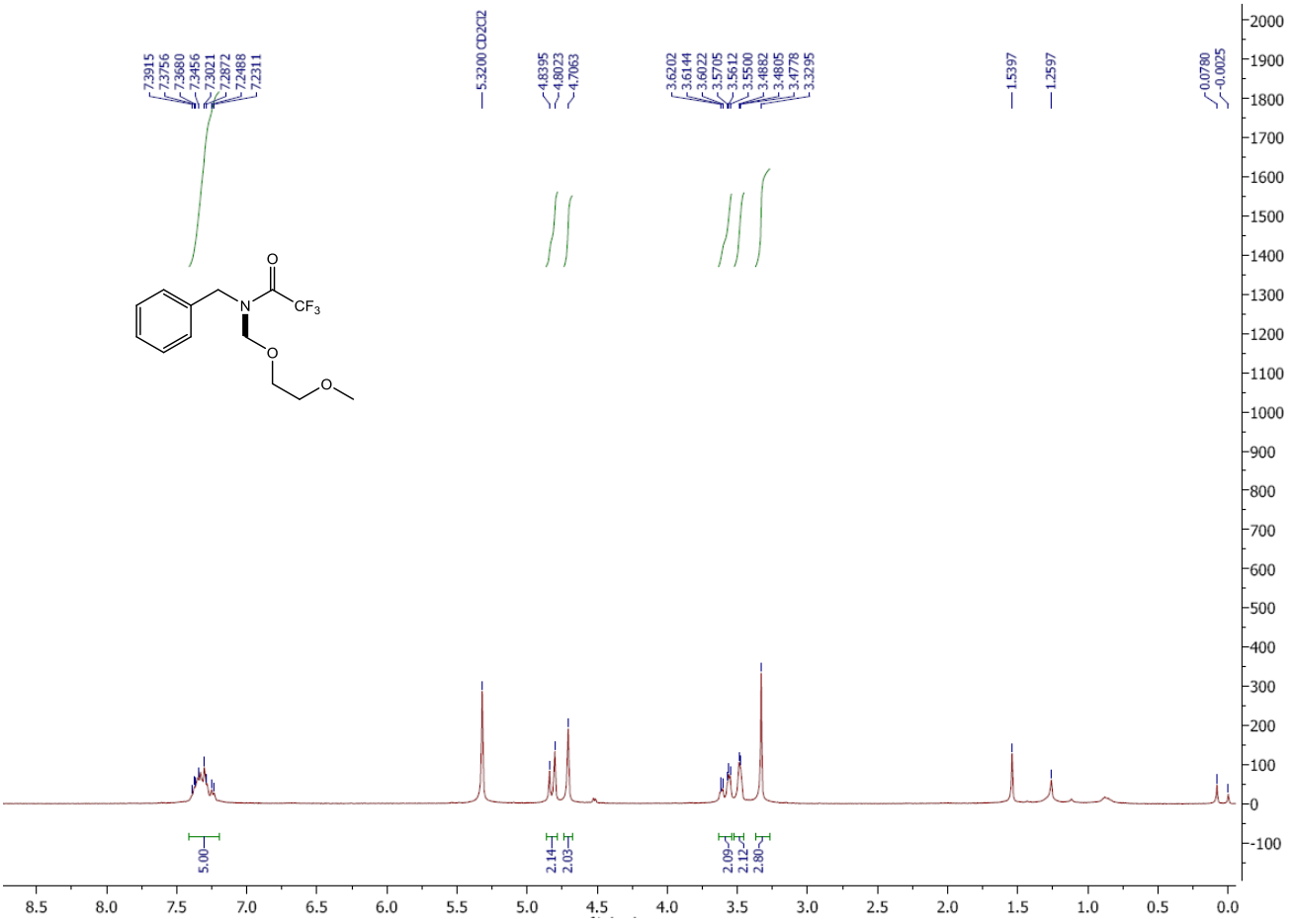


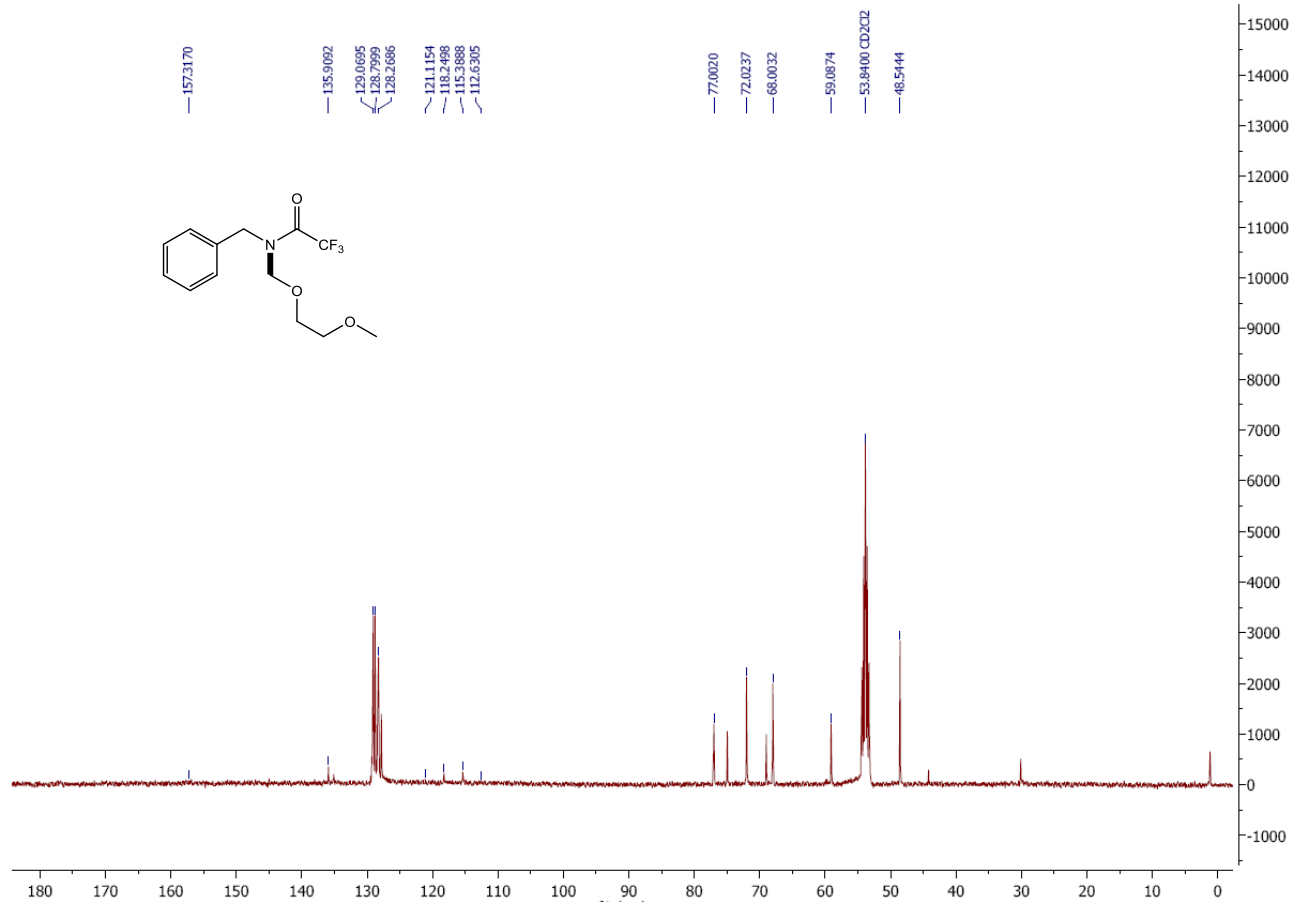
^{1}H and ^{13}C NMR spectra of N-benzyl-N-(1,2-dimethoxyethyl)-2,2,2-trifluoroacetamide (8g)



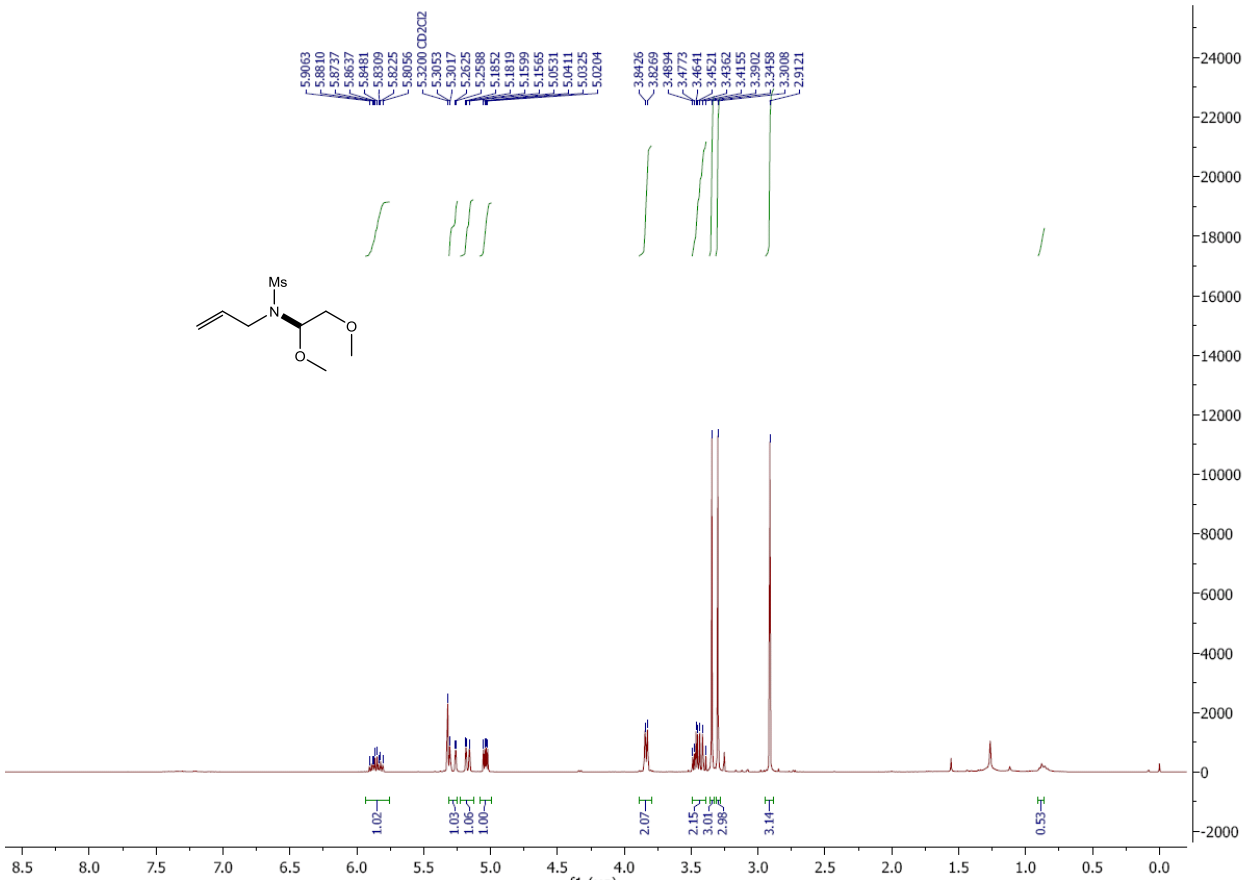


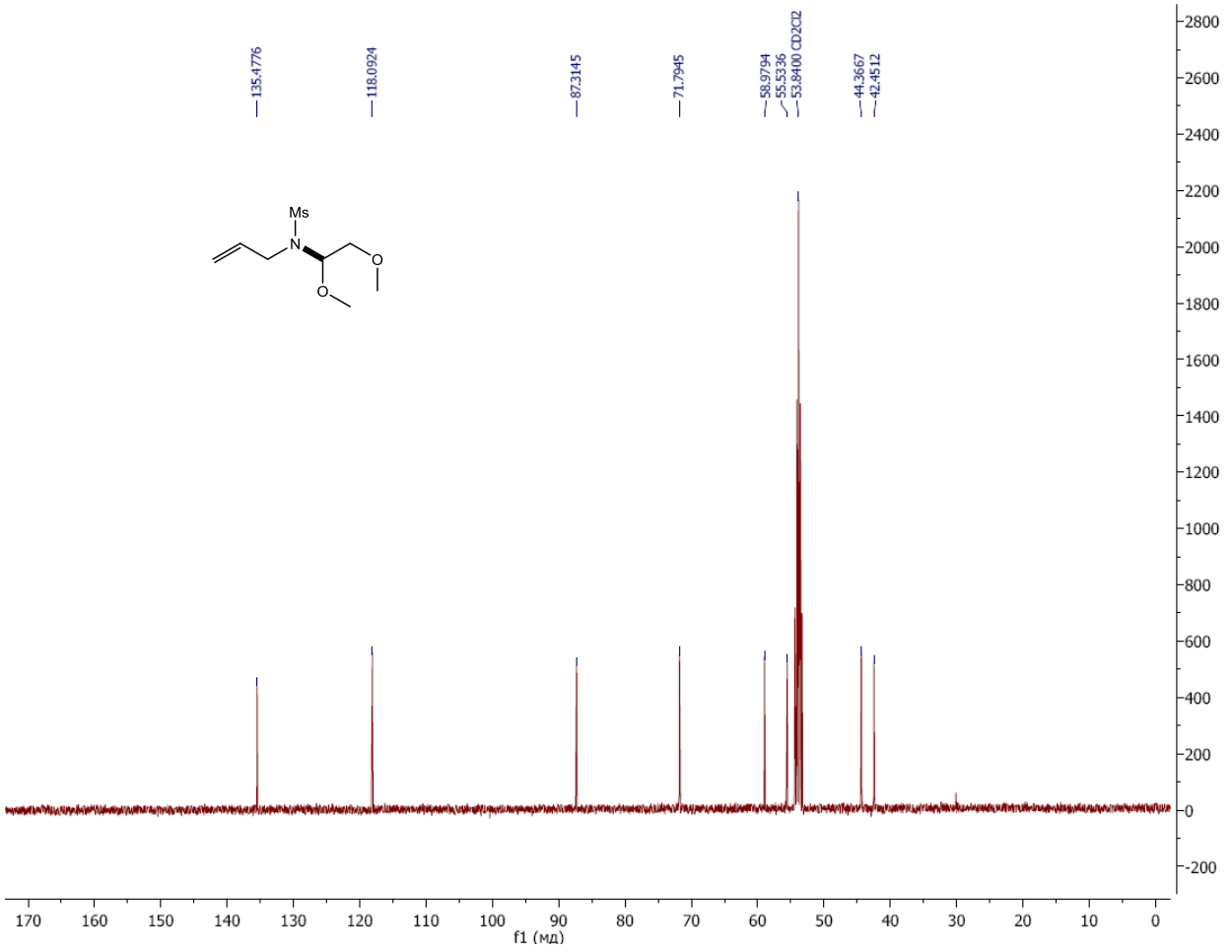
^{1}H and ^{13}C NMR spectra of N-benzyl-2,2,2-trifluoro-N-((2-methoxyethoxy)methyl)acetamide (8g')



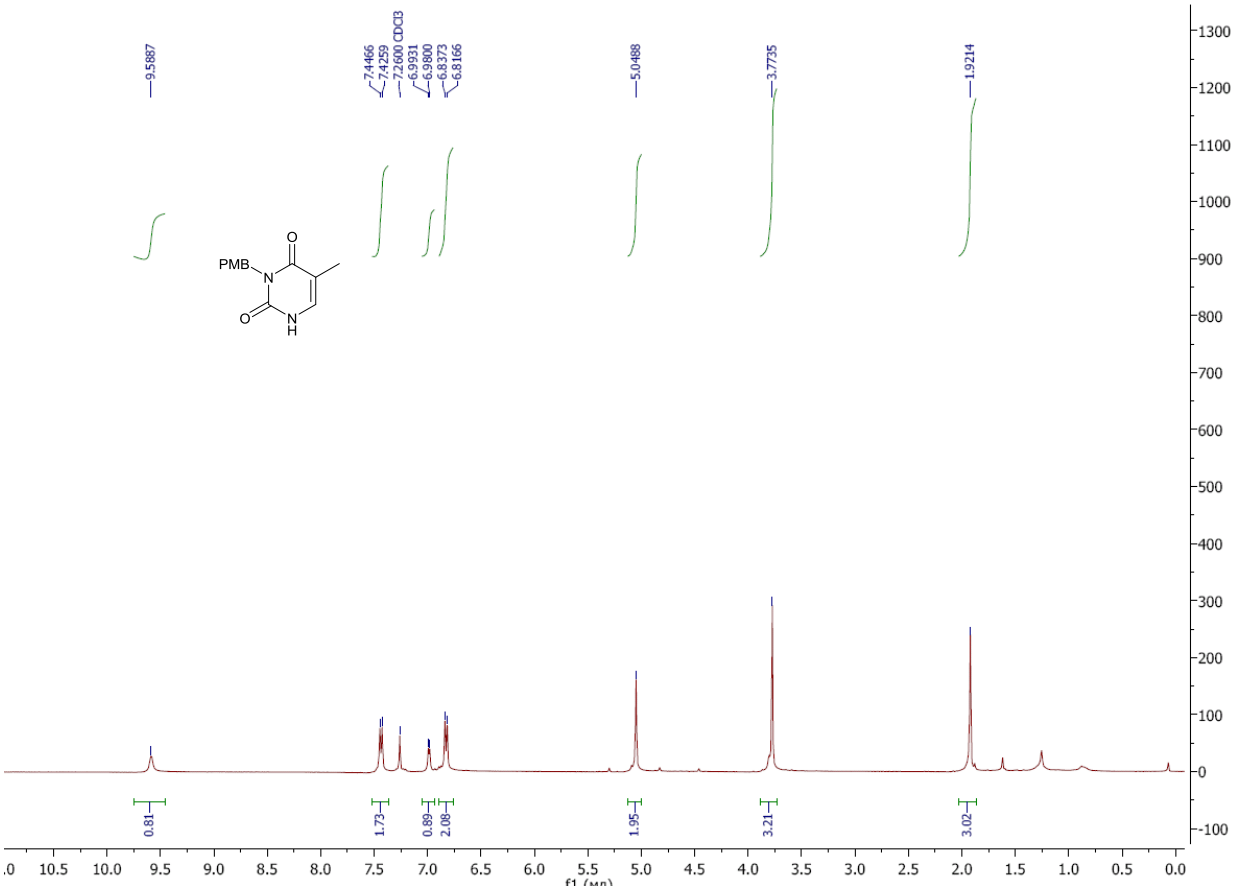


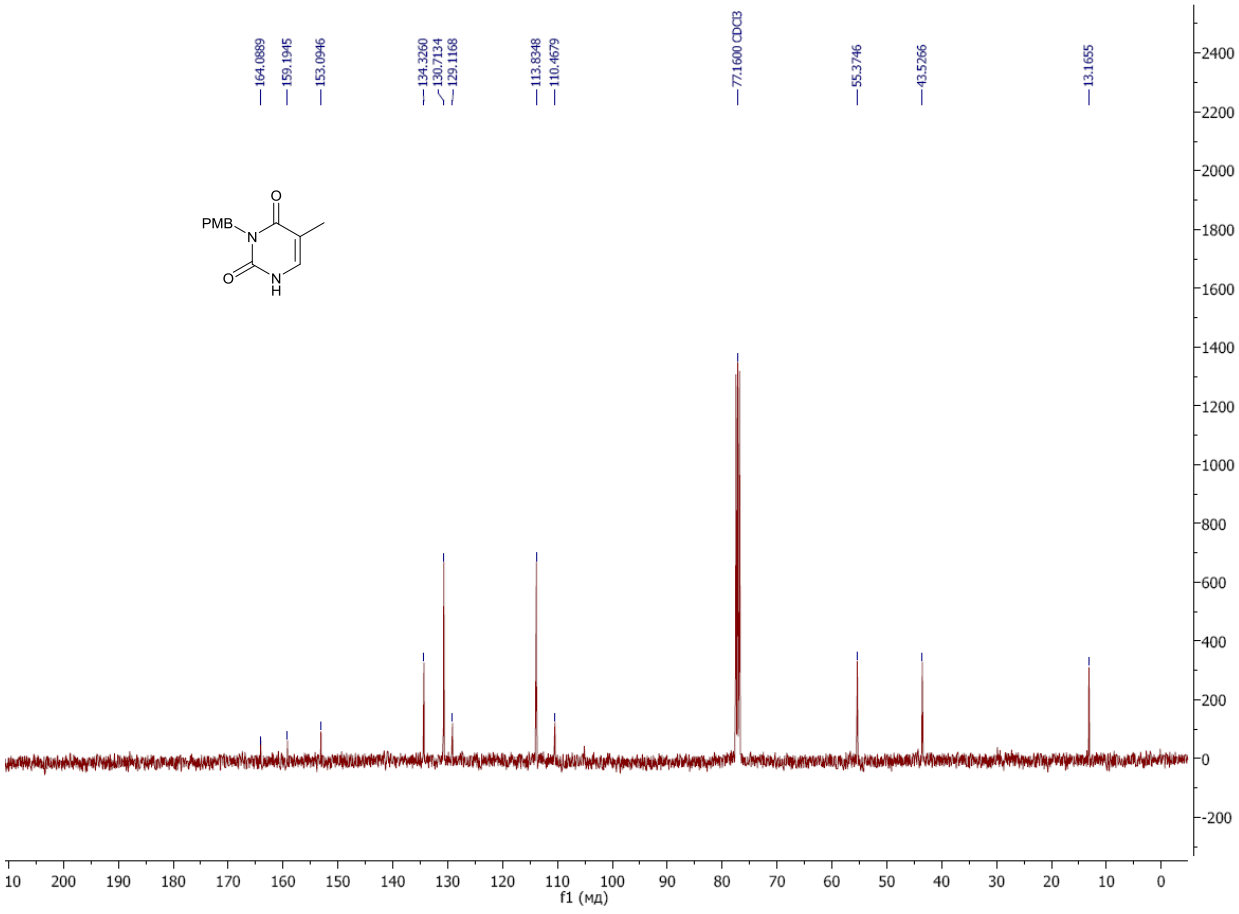
^{1}H and ^{13}C NMR spectra of N-allyl-N-(1,2-dimethoxyethyl)methanesulfonamide (8h)



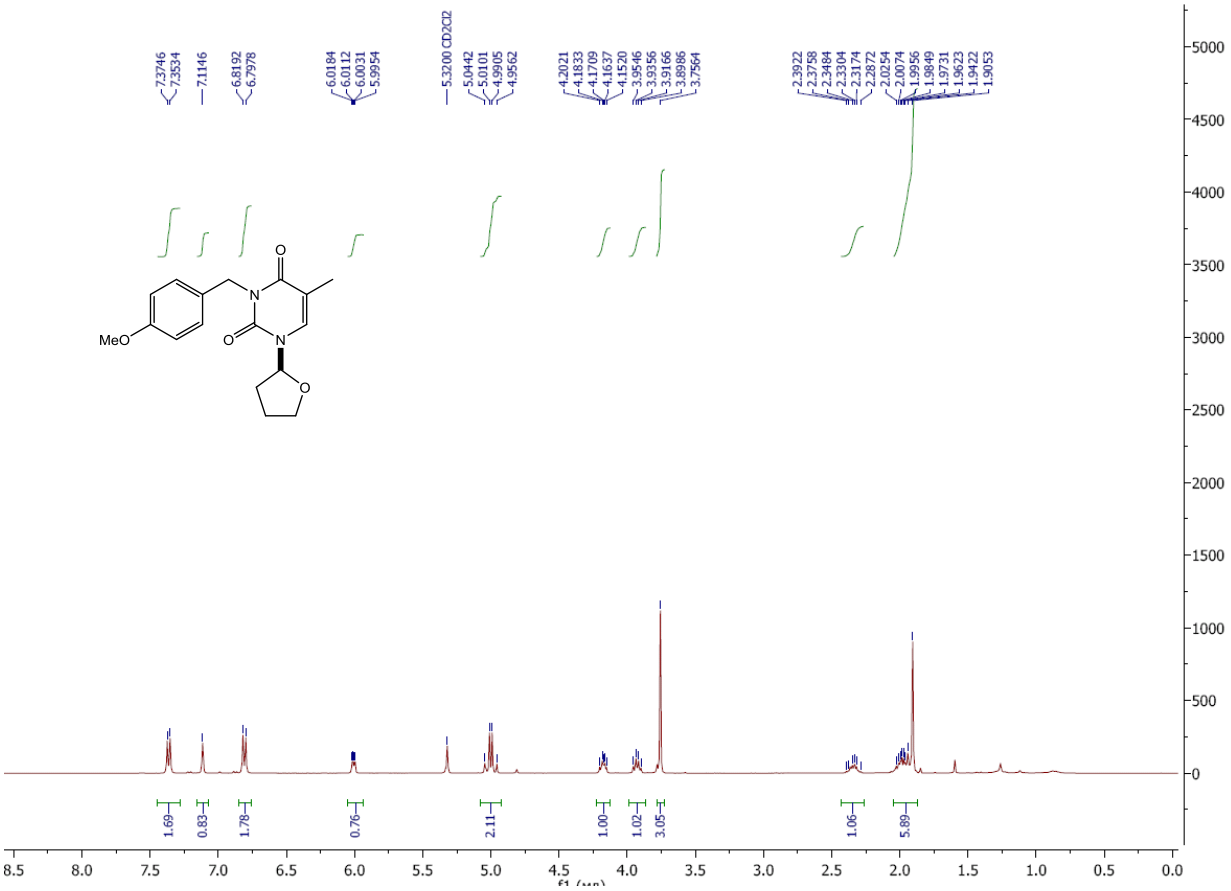


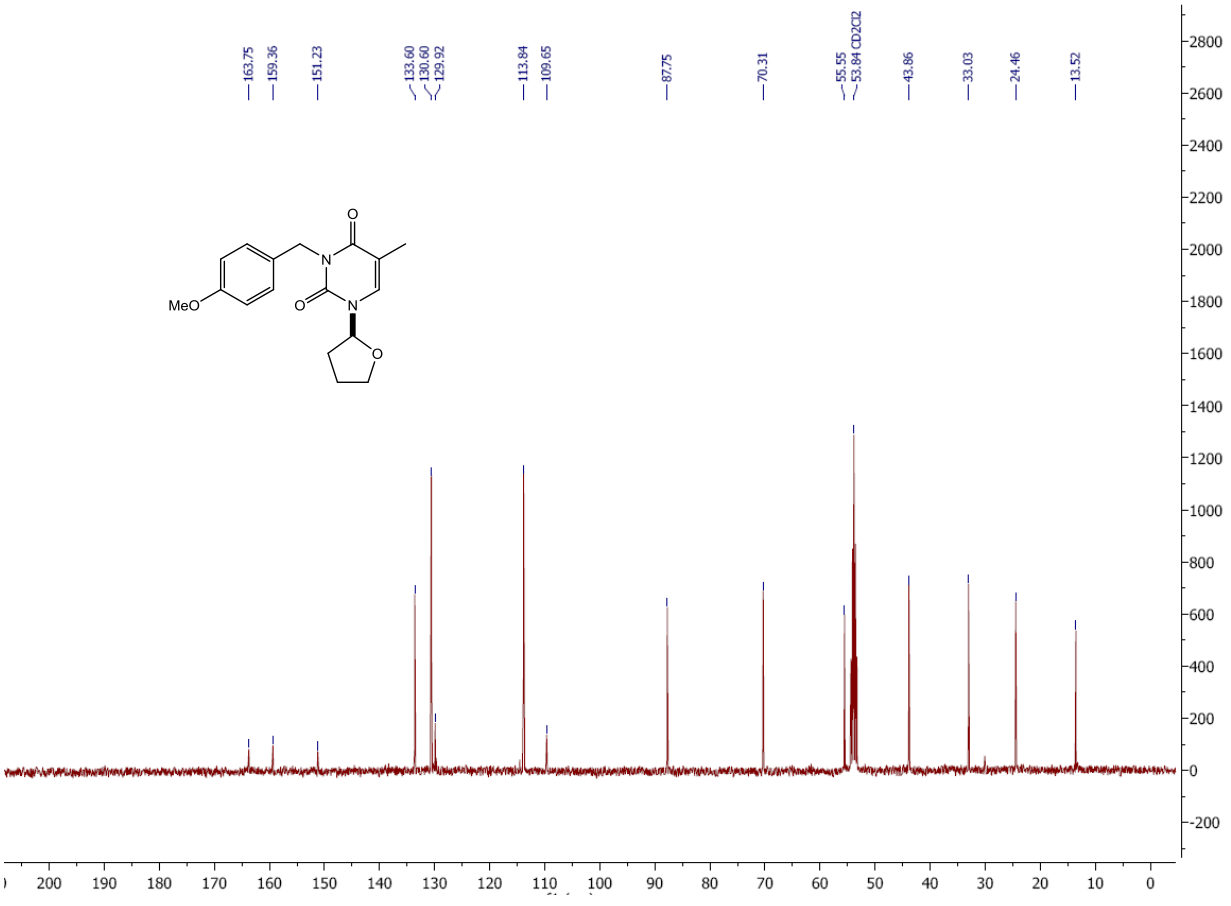
^{1}H and ^{13}C NMR spectra of 3-(4-methoxybenzyl)-5-methylpyrimidine-2,4(1H,3H)-dione (9a)



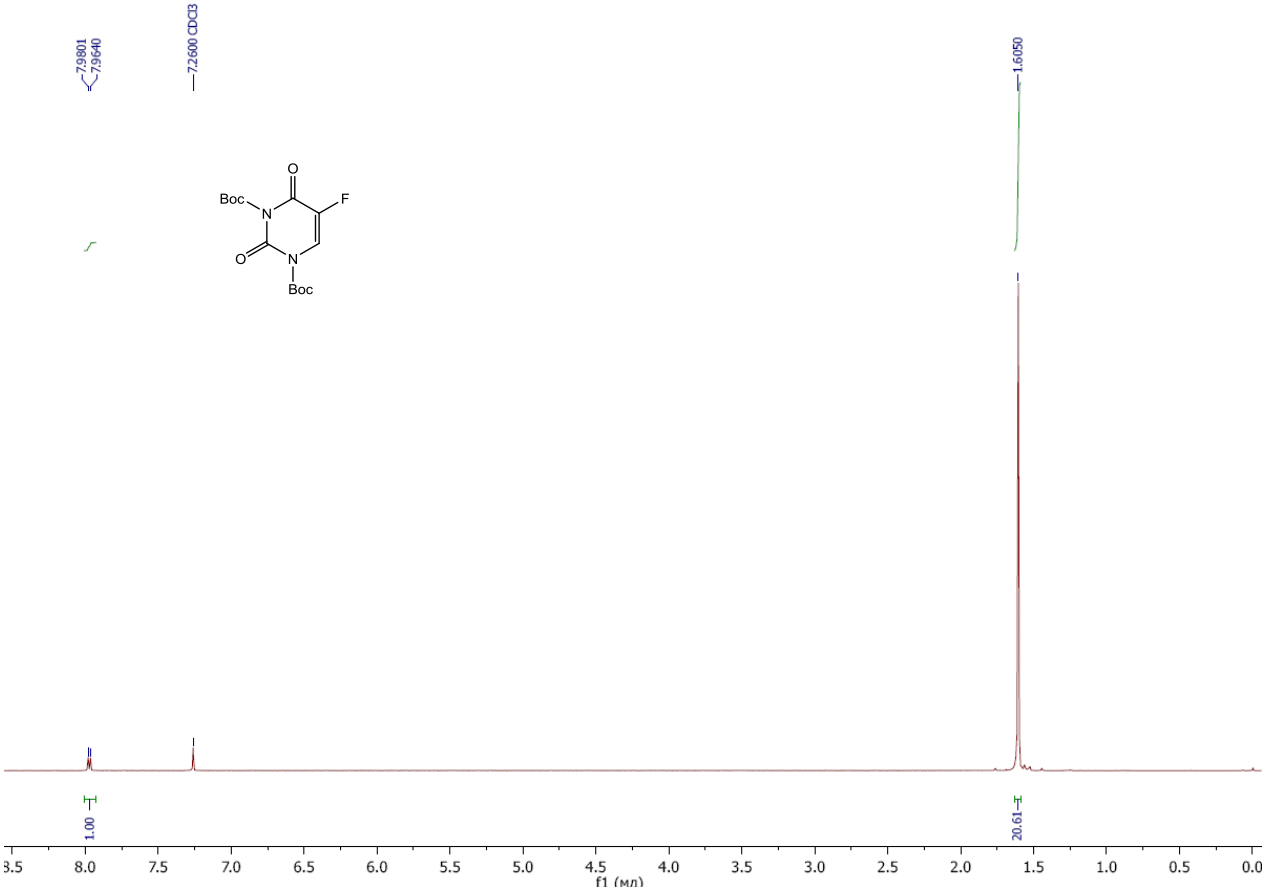


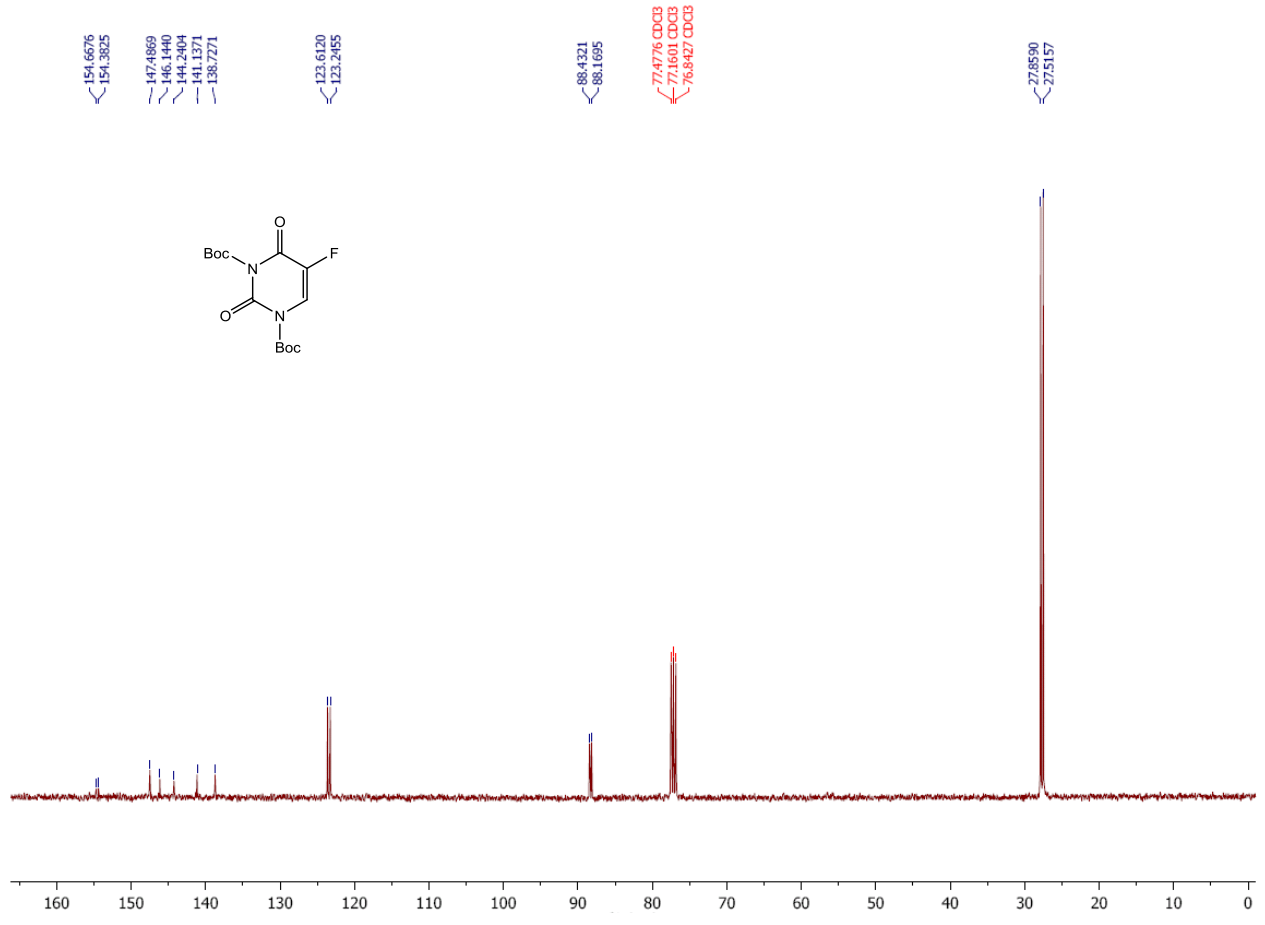
^{1}H and ^{13}C NMR spectra of 3-(4-methoxybenzyl)-5-methyl-1-(tetrahydrofuran-2-yl)pyrimidine-2,4(1H,3H)-dione (10a)



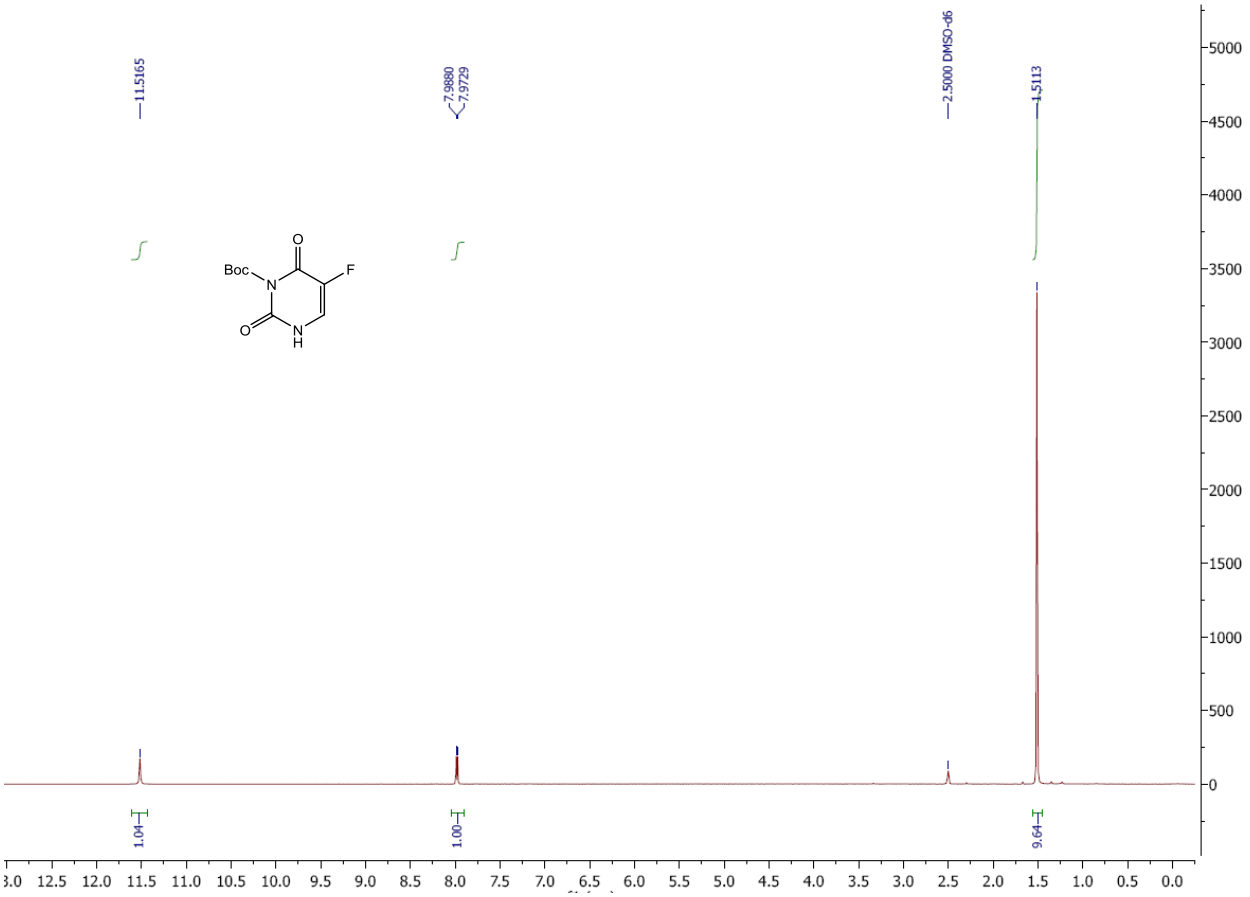


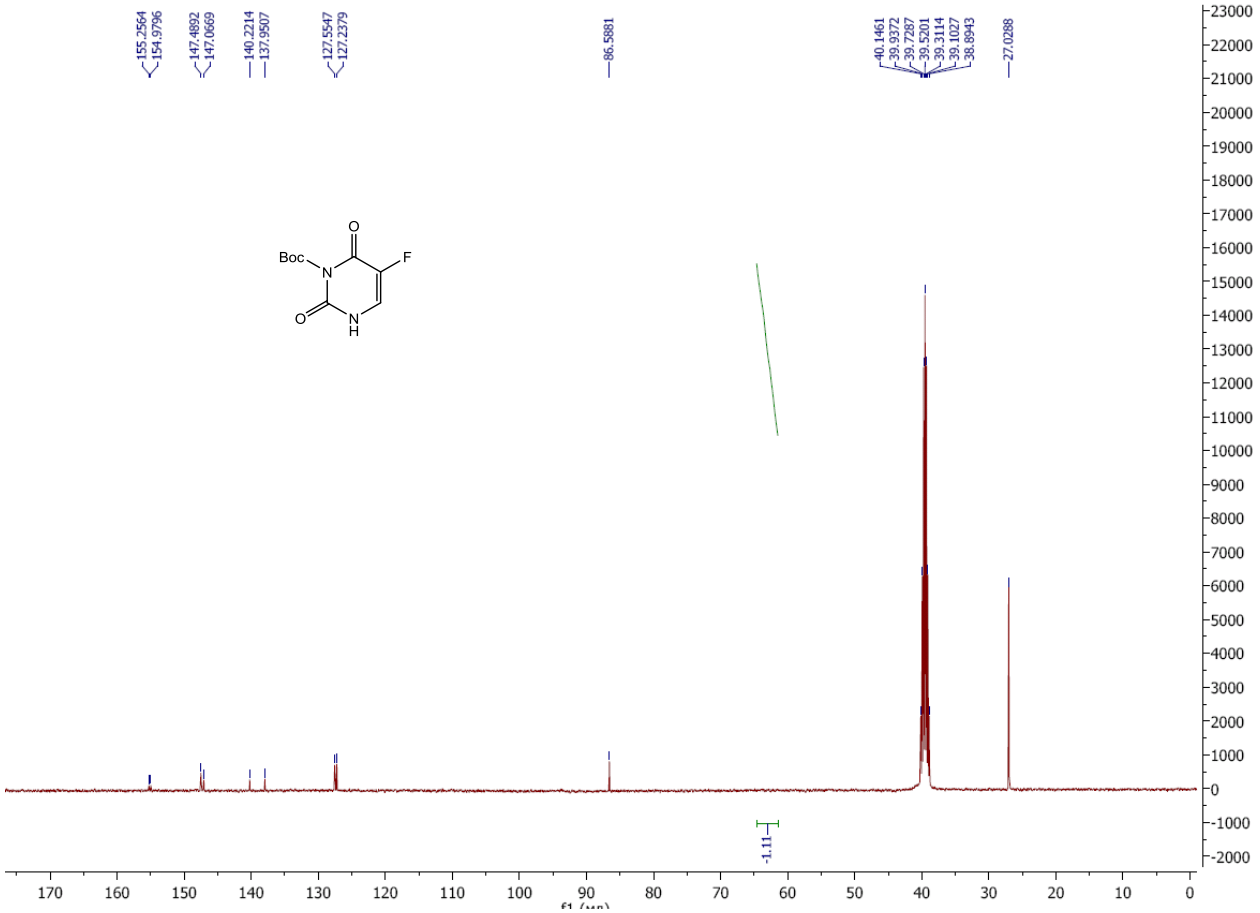
^{1}H and ^{13}C NMR spectra of di-tert-butyl 5-fluoro-2,4-dioxopyrimidine-1,3(2H,4H)-dicarboxylate (9b')



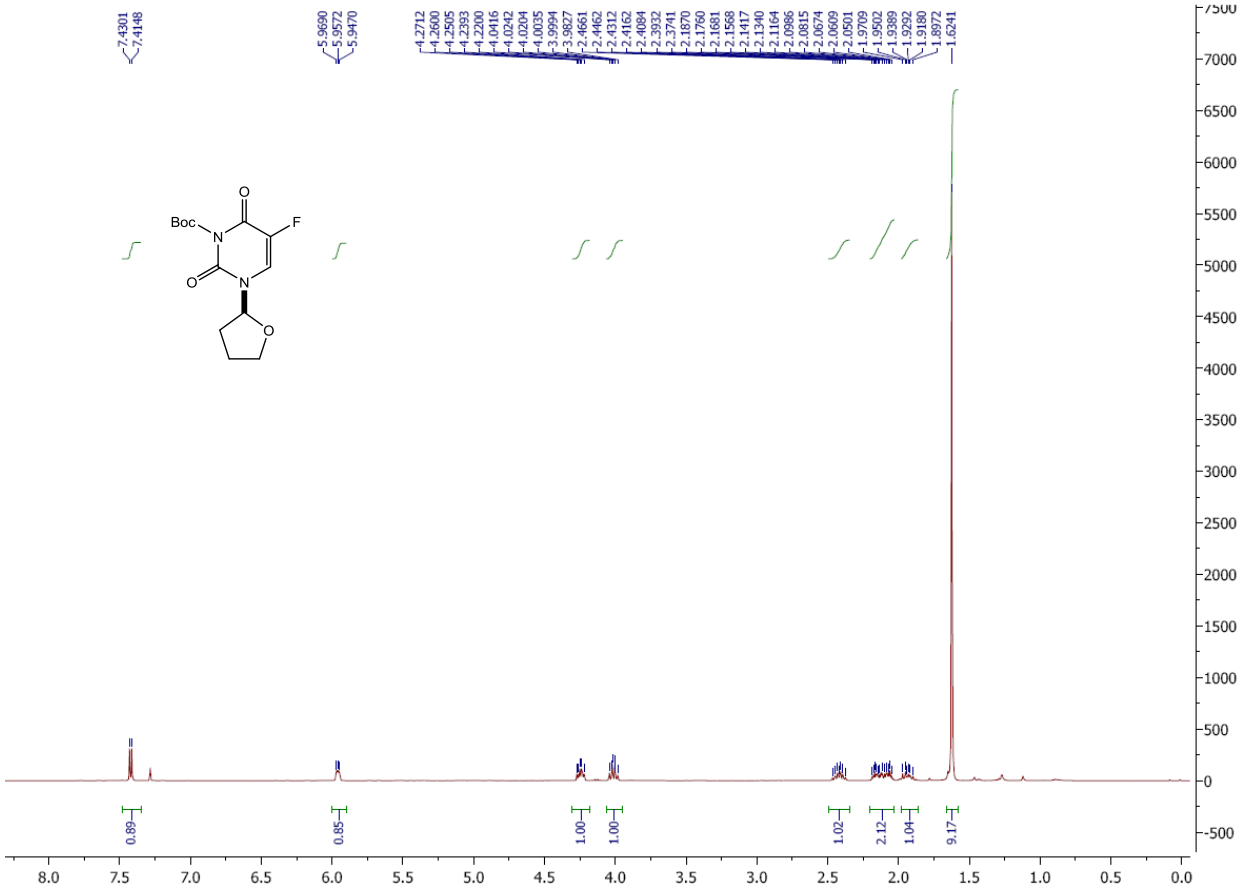


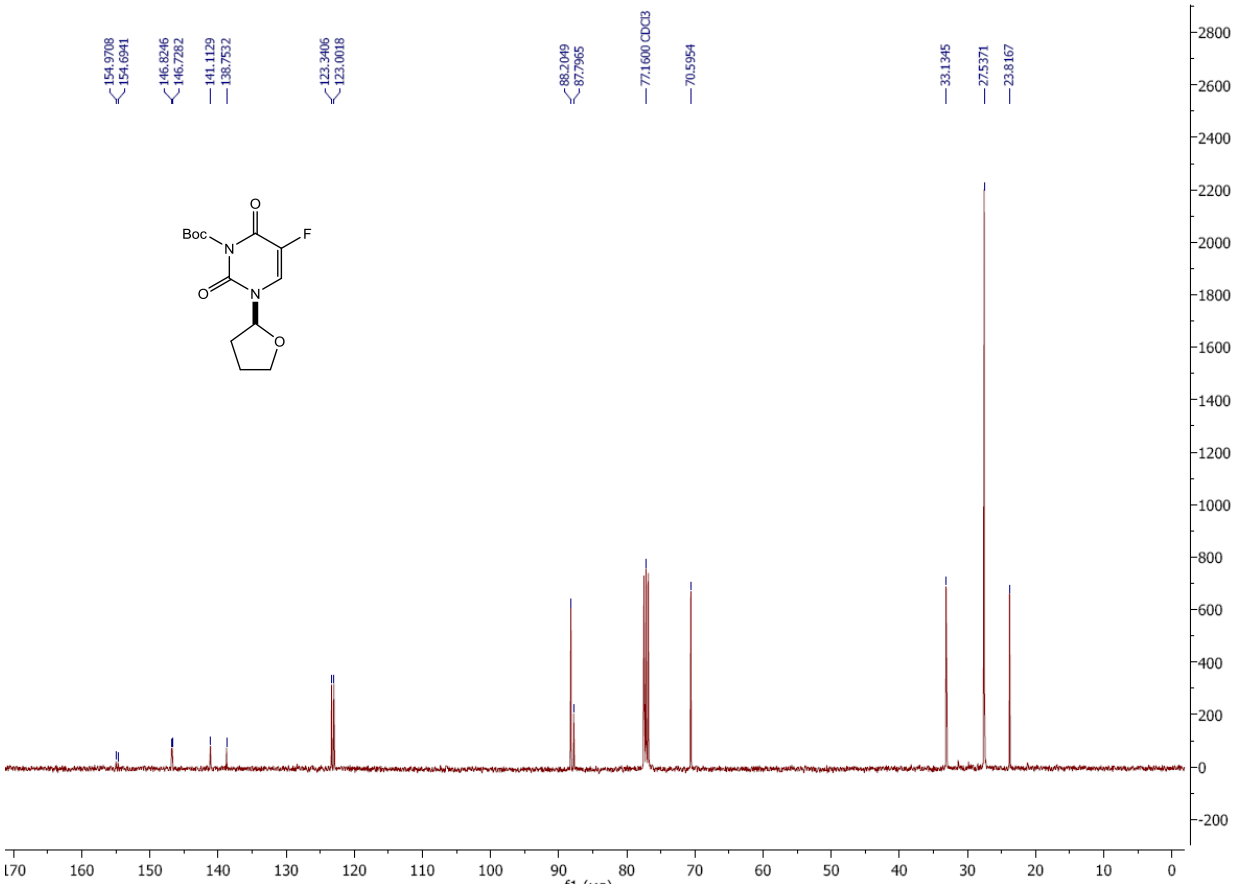
^{1}H and ^{13}C NMR spectra of tert-butyl 5-fluoro-2,6-dioxo-3,6-dihydropyrimidine-1(2H)-carboxylate (9b)



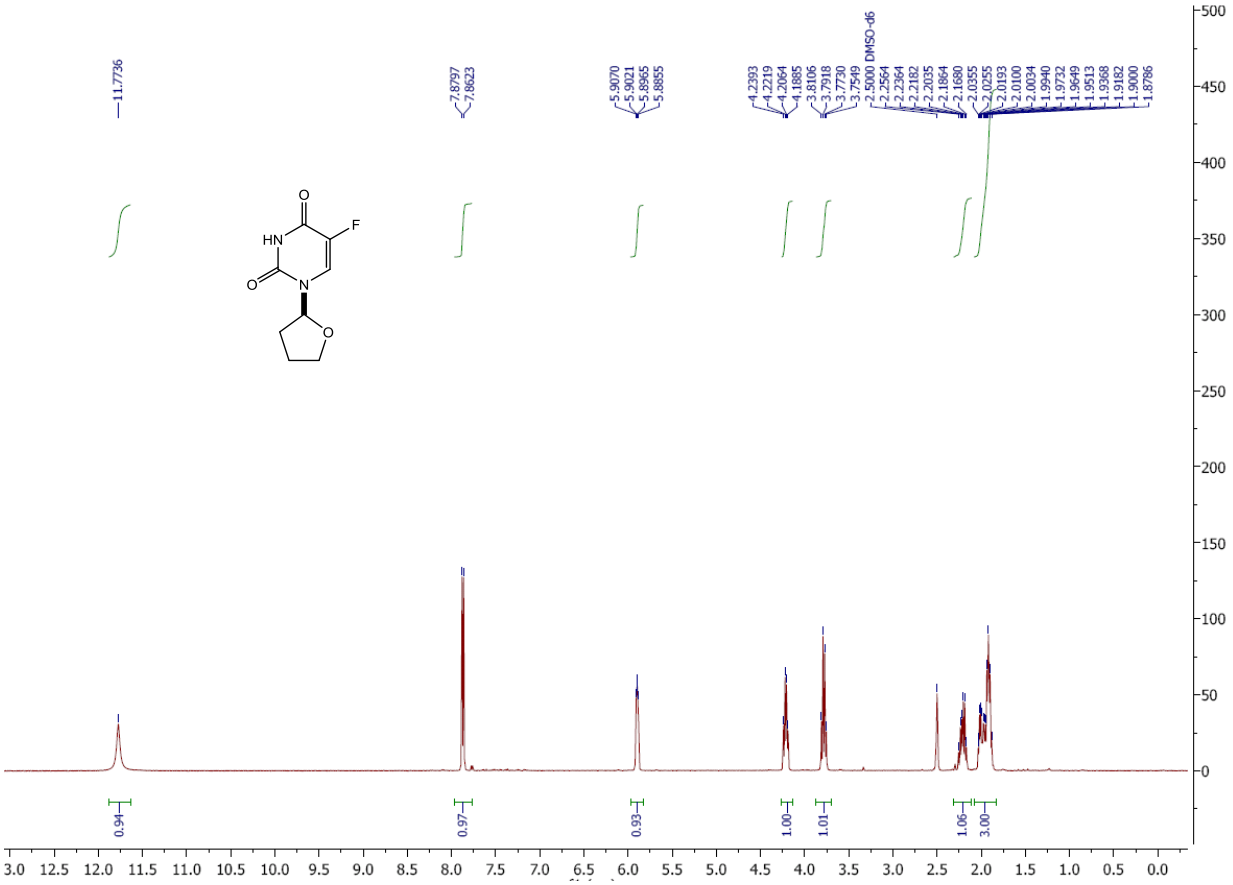


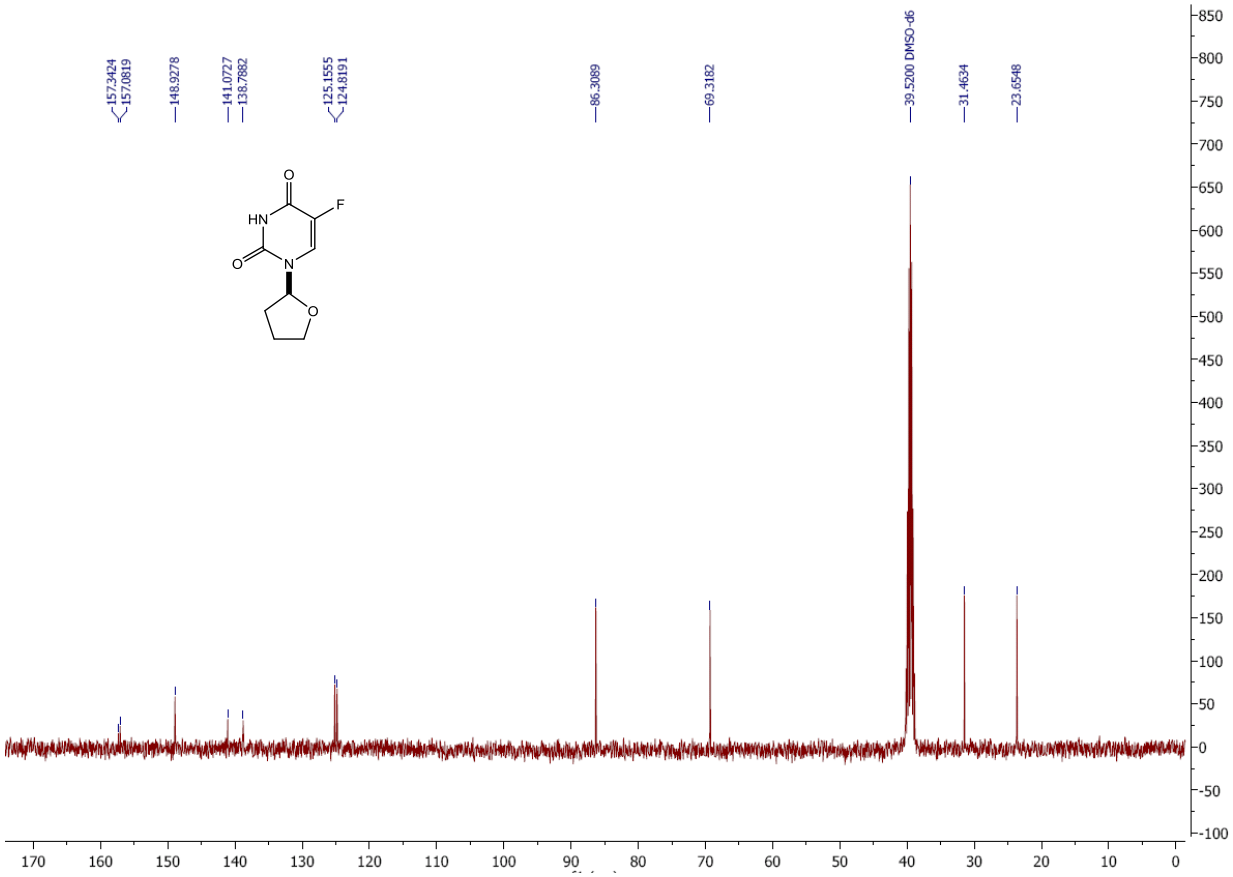
^{1}H and ^{13}C NMR spectra of tert-butyl-5-fluoro-2,6-dioxo-3-(tetrahydrofuran-2-yl)-3,6-dihydropyrimidine-1(2H)-carboxylate (10b)



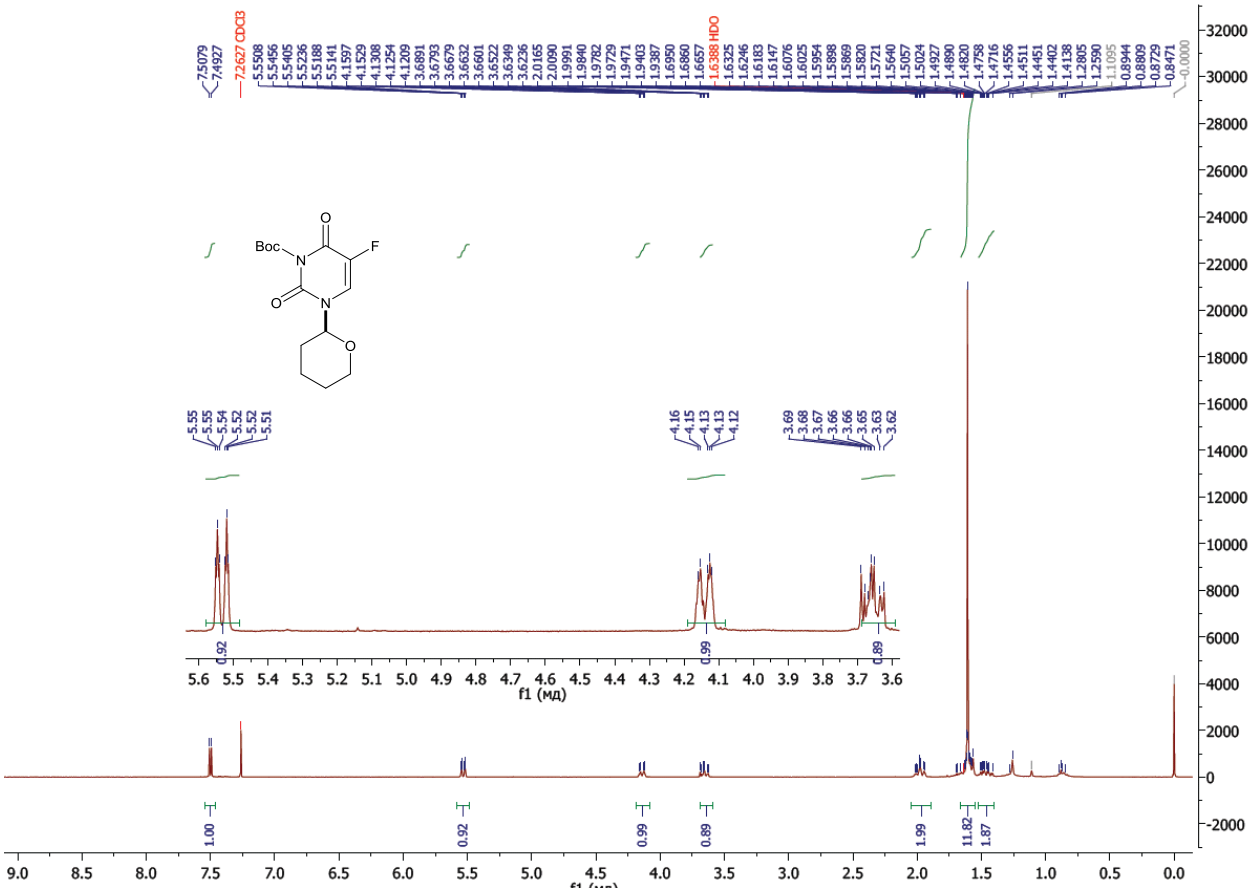


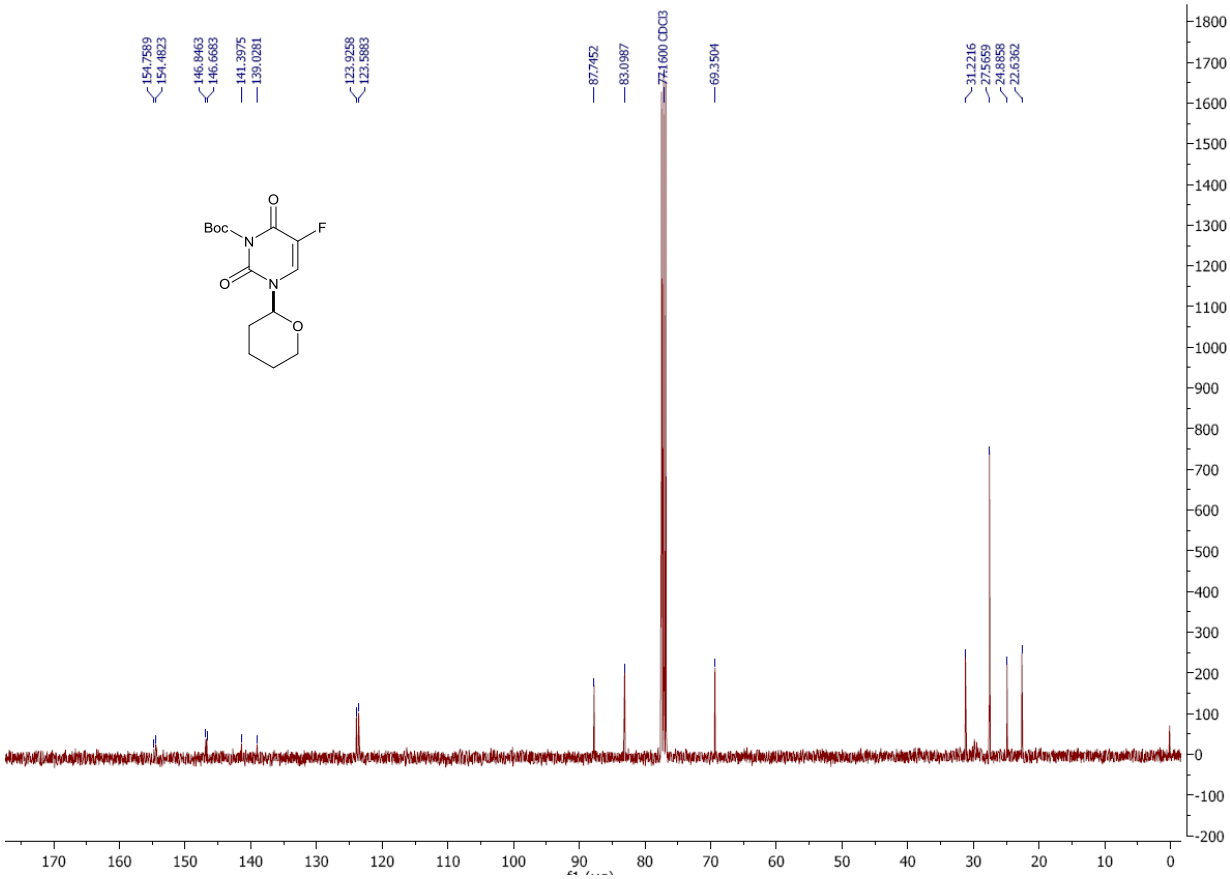
^{1}H and ^{13}C NMR spectra of 5-fluoro-1-(tetrahydrofuran-2-yl)pyrimidine-2,4(1H,3H)-dione



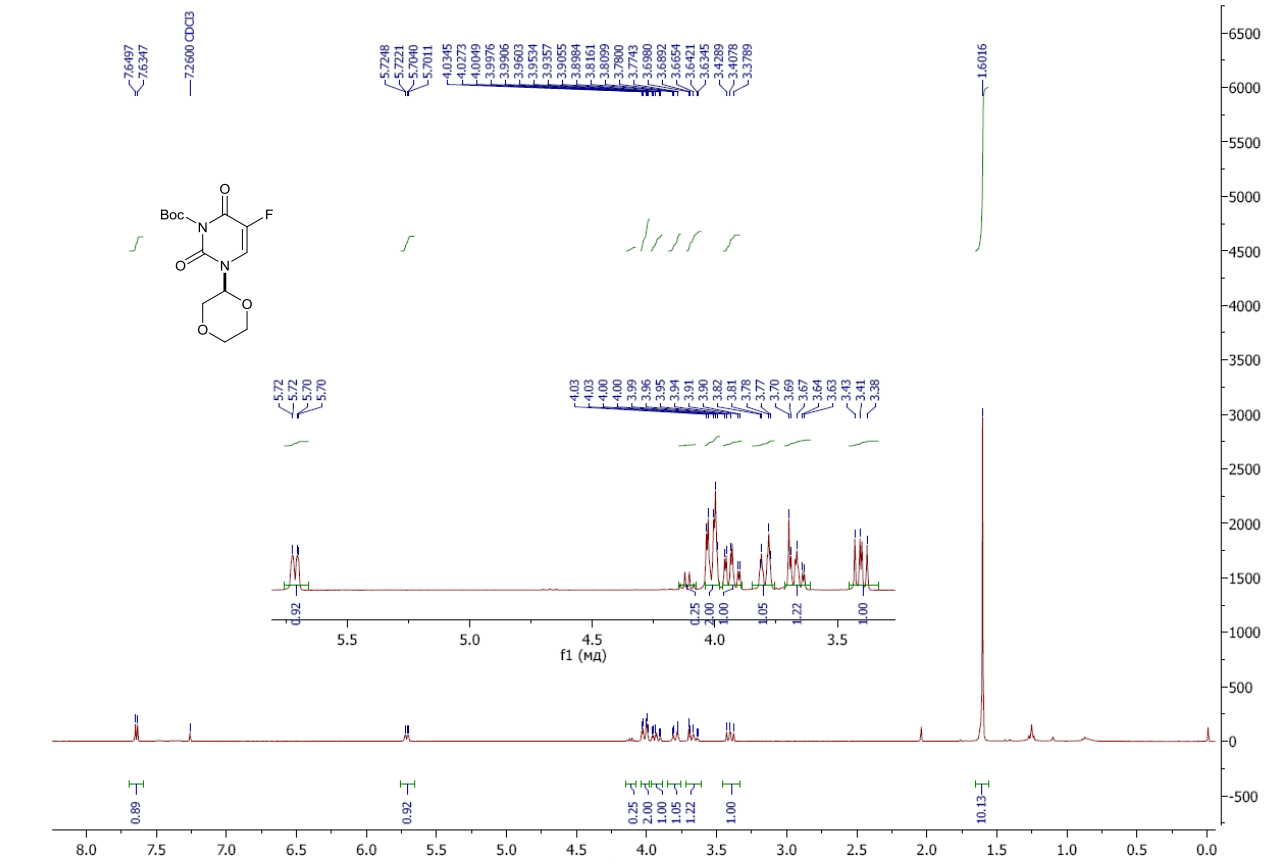


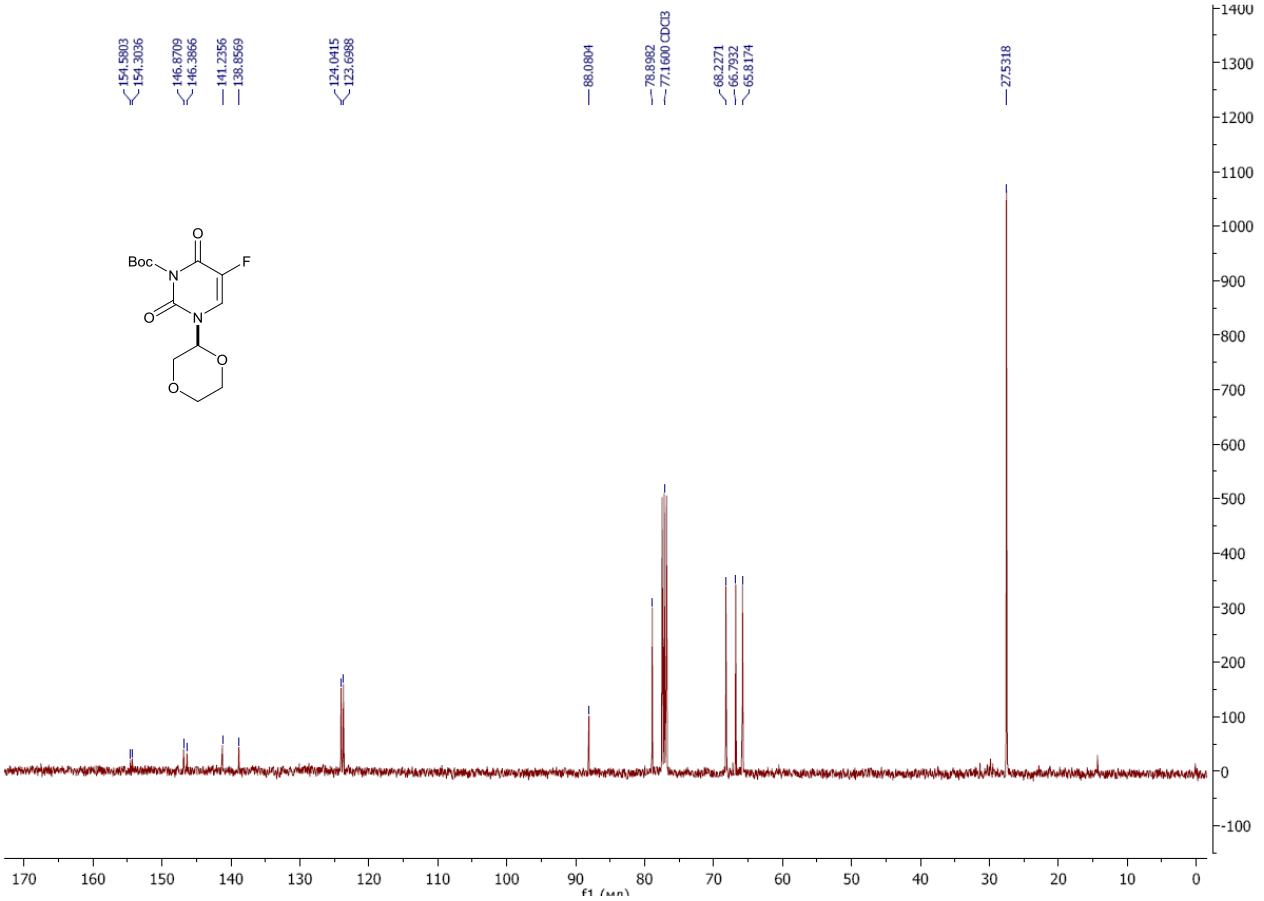
^{1}H and ^{13}C NMR spectra of tert-butyl 5-fluoro-2,6-dioxo-3-(tetrahydro-2H-pyran-2-yl)-3,6-dihydropyrimidine-1(2H)-carboxylate (10c)





^{1}H and ^{13}C NMR spectra of tert-butyl 3-(1,4-dioxan-2-yl)-5-fluoro-2,6-dioxo-3,6-dihydropyrimidine-1(2H)-carboxylate (10d)





^{1}H and ^{13}C NMR spectra of tert-butyl 3-(1,2-dimethoxyethyl)-5-fluoro-2,6-dioxo-3,6-dihydropyrimidine-1(2H)-carboxylate (10e)